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# Association of reproductive factors, sedentary behavior, and genetic factors with aging in postmenopausal women: the Women's Health Initiative

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Public Health (Epidemiology)

by

Aladdin Hassan Shadyab

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2016

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The Dissertation of Aladdin Hassan Shadyab is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California, San Diego

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2016

## DEDICATION

This dissertation is dedicated to my wonderful and loving family.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADL | Activities of Daily Living |
| BMI | Body Mass Index |
| CaD | Calcium Plus Vitamin D |
| CHD | Coronary Heart Disease |
| CI | Confidence Interval |
| CVD | Cardiovascular Disease |
| CT | Clinical Trial |
| DM | Dietary Modification |
| DNA | Deoxyribonucleic Acid |
| ES | Extension Study |
| GWAS | Genome-Wide Association Study |
| HR | Hazard Ratio |
| HT | Hormone Therapy |
| LD | Linkage Disequilibrium |
| LLS | Long Life Study |
| LTL | Leukocyte Telomere Length |
| MET | Metabolic Equivalents |
| MRC | Medical Records Cohort |
| MVPA | Moderate-to-vigorous intensity physical activity |
| OC | Oral Contraceptive |
| OPACH | Objective Physical Activity and Cardiovascular Health |
| OR | Odds Ratio |

| | |
|---|---|
| OS | Observational Study |
| SAS | Statistical Analysis Software |
| SD | Standard Deviation |
| SNP | Single Nucleotide Polymorphism |
| VM | Vector Magnitude |
| WHI | Women's Health Initiative |

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I would like to thank the Women's Health Initiative for granting me access to their data for my dissertation. I would also like to thank the following co-authors and investigators for their contributions to my dissertation: Dr. Margery Gass, Dr. Molly Waring, Dr. Marcia Stefanick, Ms. Mary Pettinger, Dr. Charles Kooperberg, Dr. Alexander Reiner, Dr. JoAnn Manson, Mr. Chancellor Hohensee, Dr. Cara Carty, Ms. Jingmin Liu, Dr. Eileen Rillamas-Sun, Dr. Chongzhi Di, Dr. Todd Manini, Dr. Michael LaMonte, Dr. Lifang Hou, and Dr. Abraham Aviv. The opinions, ideas, and interpretations included in this dissertation are those of the co-authors and not those of the WHI investigators.

Chapter 2, in full, has been submitted for publication of the material as it may appear in *Journal of the American Medical Association*. Shadyab, Aladdin H.; Macera, Caroline A.; Shaffer, Richard A.; Jain, Sonia; Gallo, Linda C.; Gass, Margery L.S.; Waring, Molly E.; Stefanick, Marcia L.; LaCroix, Andrea Z. The dissertation author was the primary investigator and author of this paper.

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3. Vyas K, **Shadyab AH**, Lin CD, Crum-Cianflone NF. Trends and Factors Associated with Initial and Recurrent Methicillin-Resistant *Staphylococcus aureus* (MRSA) Skin and Soft-Tissue Infections among HIV-Infected Persons: An Eighteen-Year Study. *Journal of the International Association of Providers in AIDS Care* 2014;13:206-213.
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2. Vyas K, **Shadyab AH**, Lin CD. Crum-Cianflone NF. Trends and Factors Associated with Initial and Recurrent Methicillin-Resistant *Staphylococcus aureus* Skin and Soft-Tissue Infections among HIV-Infected Persons: An Eighteen-Year Study. 19th Annual International AIDS Conference, Washington DC, July 22-July 27, 2012.
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## ABSTRACT OF THE DISSERTATION

Association of reproductive factors, sedentary behavior, and genetic factors with aging in postmenopausal women: the Women's Health Initiative

by

Aladdin Hassan Shadyab

Doctor of Philosophy in Public Health (Epidemiology)

University of California, San Diego, 2016
San Diego State University, 2016

Professor Andrea Z. LaCroix, Chair

**Background**: In the United States, the aging population is rapidly growing. By 2060, it is expected that 12 million women will be ages 85 years and older. However, determinants of longevity and healthy aging in women are not fully understood. This

dissertation had three objectives: 1) Determine whether ages at menarche and menopause and reproductive lifespan were associated with survival to age 90, termed "exceptional longevity;" 2) Determine whether genetic factors associated with longevity in prior studies among populations of European descent were associated with survival to ages 85 and 90 and healthy aging in white, African-American, and Hispanic women; and 3) Determine whether accelerometer-measured and self-reported sedentary time were associated with leukocyte telomere length (LTL), a purported biomarker of aging, among older women.

**Methods**: Three studies were conducted among participants from the Women's Health Initiative, a longitudinal study investigating major determinants of chronic diseases in postmenopausal women. Study one was a prospective study among 16,251 women who had potential to survive to age 90 as of August 29, 2014. Study two was a prospective study among 11,154 women who could survive to age 85 as of August 29, 2014 and used genetic data from multiple genome-wide association studies. Study three was a cross-sectional study among 1,481 women with information on either accelerometer-measured or self-reported sedentary time. All studies consisted of racially diverse samples.

**Results**: In study one, the odds of exceptional longevity were elevated among women with later menarche, later menopause, and longer reproductive lifespan. In study two, three variants at *APOE* were associated with survival to age 90 and healthy aging in white women, and seven variants at a novel locus were associated with survival to age 85 in Hispanic women. In study three, among women at or below the median level of moderate-to-vigorous intensity physical activity (MVPA), higher accelerometer-

measured sedentary time was associated with shorter LTL. Among women with higher MVPA levels, sedentary time was not associated with LTL.

**Conclusions**: Findings suggest that reproductive and genetic factors may be associated with late-age survival and that a high level of inactivity may be associated with short LTL.

# CHAPTER 1: INTRODUCTION

**The Epidemiology of Longevity**

Throughout the past century, the United States has experienced a rapid increase in the aging population due to declines in fertility and lower mortality rates at older ages.[1,2] In 2010, there were over 40 million people in the United States ages 65 and older, and by 2050, it is expected that 83 million people will be in this age group. The "oldest-old," or persons ages 85 and above, are currently experiencing the fastest rate of growth and now represent approximately 2% of the US population.[3] In 1900, there were 122,000 oldest-old individuals living in the United States, and by 2010, there were 5.5 million people in this age group with an expected increase to 18 million by 2050. Finally, among the oldest-old population, nonagenarians are experiencing the fastest rate of growth; the number of people in this age group is expected to quadruple in the next 40 years.[3]

The current aging epidemic has created an important public health challenge for the 21st century. The gain in life expectancy – which is largely due to improvements in public health, nutrition, education, and medicine – has led to concern about whether the aging population is able to delay disease, functional limitations, and disability, often termed "healthy" or "successful" aging.[3] Consequently, there is great interest as to which factors and mechanisms contribute to longevity and successful aging.

The lifespan of women is longer than that of men.[3] By 2060, it is expected that 12 million women will be ages 85 years and older.[4] However, determinants of longevity and healthy aging among women are not fully understood. Longevity may be multifactorial; reproductive factors (e.g., age at menopause), genetic factors, and lifestyle behaviors (e.g., physical activity) may all be important determinants of a woman's lifespan.[3]

**Ages at Menarche and Menopause and Health Outcomes**

Ages at menarche and menopause have been largely studied in relation to mortality and age-related diseases.[5-10] However, it is currently unknown whether these reproductive factors are determinants of longevity. Average age at menarche ranges from 12-13 years, and secular trends throughout the past fifty years have been showing decreases in age at menarche.[11,12] Age at menarche may be influenced by several factors including race/ethnicity, body mass index (BMI), socioeconomic status, and genetic factors.[13,14]

In prior studies, early menarche has been associated with increased risk of all-cause mortality, cardiovascular disease, and type 2 diabetes.[5-7] In a 37-year cohort study of >61,000 Norwegian women, a 2.4% reduction in mortality risk for every one year increase in age at menarche was observed.[5] In a population-based study in the United Kingdom involving >15,000 women, those with menarche at <12 years of age had increased risk of hypertension (HR, 1.13; 95% CI, 1.02-1.24), cardiovascular disease (HR, 1.17; 95% CI, 1.07-1.27), all-cause mortality (HR, 1.22; 95% CI, 1.07-1.39), and cardiovascular mortality (HR, 1.28; 95% CI, 1.02-1.62), independent of factors including demographics, lifestyle behaviors, and use of hormone therapy.[6]

Menopause is defined as the cessation of menstruation resulting from a loss of ovarian follicles.[15] In white women, the median age at which menopause occurs is 50 years[15], and secular trends have been showing increases in age at menopause.[12] The timing of menopause may be due to genetic, social, environmental, and hormonal factors.[16-18]

Early age at menopause has been linked to an increased risk of all-cause mortality, coronary heart disease, and type 2 diabetes.[8-10] For example, in a 37-year follow-up study of >19,000 Norwegian women, a 1.6% reduction in mortality risk for every three-year increase in age at menopause was observed.[8] Surgical menopause has also been studied in relation to mortality, but findings have been inconsistent.[19,20] Finally, it has been suggested that longer reproductive lifespan, representing the difference between ages at menopause and menarche, may be associated with decreased risk of mortality due to longer exposure to endogenous estrogen.[21]

To date, no study has assessed the association of reproductive factors with late-age survival. If a strong relationship between slower reproductive aging and longer lifespan is demonstrated, then reproductive factors may be considered as potential biomarkers of aging and thus may be used in the clinical setting when determining a woman's chances of long-term survival. This may have important public health implications, as reproductive factors may then be used as surrogates of long life in future studies of aging.

**Genetic Factors Associated with Longevity**

Attaining longevity may be partially due to genetic factors, with a heritability estimate of 20%-35%.[22] Previous candidate gene association studies have observed that only variants of two genes, *APOE* and *FOXO3A*, are consistently associated with longevity.[22] Apolipoprotein E is a major carrier of cholesterol with three common polymorphic alleles (ε2, ε3, and ε4) and six possible genotypes.[23] The ε4 allele has been associated with increased risk of Alzheimer's disease.[24] The ε2 allele has been shown to

be present at a higher frequency in centenarians, whereas the ε4 allele is less frequent in this group.[25] A study in a diverse sample consisting of Spanish, Italian, and Japanese centenarians observed that the ε4 allele reduced the odds of longevity by 45%-65%, while the ε2 allele increased the odds of longevity by a factor of two.[26]

The forkhead box O3A (*FOXO3A*) gene encodes a transcription factor and is involved in the insulin/insulin-like growth factor 1 pathway; its effect on longevity may be mediated by oxidative stress.[3] A prior study among Japanese-American men observed significantly different *FOXO3A* genotype frequencies when comparing those aged 95 years or older with dead controls.[27] However, as this study consisted only of Japanese men, findings may not be generalized to other ethnic groups or women. Variation at *FOXO3A* was also associated with centenarian status in a study comparing German long-lived cases (95-110 years old) with younger controls (60-75 years old), but men and women were not examined separately.[28]

In most prior genome-wide association studies (GWAS) of longevity, significant associations at genetic variants besides those near *APOE* have not been observed.[22] However, a recent meta-analysis of GWAS findings observed a significant association with survival to age 90 or above at a novel locus (rs2149954 on chromosome 5q33.3).[29] Carriage of the minor allele at this SNP was associated with a lower risk of all-cause and CVD mortality. The study population consisted largely of white women, but it is currently unknown whether this novel locus is also associated with longevity in other racial/ethnic groups.

Previous studies evaluating the relationship between genetic factors and longevity were limited by several factors, including failure to use birth-cohort matched controls;

consequently, findings have been biased by cohort effects. Studies have also failed to examine men and women separately. Further, no study to date has determined whether genetic factors are associated with longevity in African-Americans or Hispanics. Finally, the relationship between genetic factors and healthy aging, that is, surviving free of morbidity and disability, is currently unknown.

**Sedentary Time and Leukocyte Telomere Length**

Telomeres are repetitive DNA-protein complexes located at the end of linear chromosomes that protect and maintain genomic stability.[30] During each cell division, telomeres progressively shorten, leading to cellular senescence or apoptosis. The subsequent loss of cell viability resulting from shortened telomeres has been linked to many age-related diseases (e.g., cancer, heart disease) and decreased lifespan.[30,31] Telomere shortening is triggered by oxidative stress and inflammation, and represents lifetime exposure to oxidative and inflammatory damage.[32] Therefore, shortened telomeres represent a "molecular clock" and may be considered as potential biomarkers of cellular aging. Typically, studies measure leukocyte telomere length (LTL) as a surrogate for telomere length in all tissues.[33]

Some studies have suggested that LTL may be modified by environmental and lifestyle factors. Factors previously associated with short LTL include inadequate levels of physical activity, smoking, and obesity.[34-36] However, sedentary time – which is characterized by activities involving low energy expenditure such as sitting, lying down, and watching television – has not been extensively studied in relation to LTL.[35,37] A cross-sectional study in 7,813 Nurses' Health Study participants aged 43-70 years found

that total sitting time and time spent in specific types of sitting were not associated with LTL after adjustment for covariates including physical activity and BMI.[35] A recent study among 49 individuals participating in a randomized clinical trial on physical activity found that in the intervention group, which consisted of sedentary, overweight, 68-year old women, reduced sitting time was associated with increased LTL after 6 months.[37] However, these studies did not assess objectively-measured sedentary time (i.e., measured by accelerometer), which does not correlate with self-reported data.[38] Additionally, these studies did not measure LTL using Southern blot techniques, which are considered the "gold standard".[39] Finally, these studies did not perform analyses in diverse samples. Understanding the relationship between sedentary time and LTL in different populations is important, given that LTL may be a potentially modifiable biomarker of aging linked to many age-related diseases.

Sedentary time is of current public health importance as it has emerged as a risk factor for deleterious health outcomes including obesity, type 2 diabetes, and all-cause mortality independent of physical activity.[40,41] However, its effect on aging at the cellular level, particularly in older adults, is currently unclear. Sedentary time is highly prevalent in older adults, and self-reported data indicate that older adults spend on average 5.3 hours of their waking days sedentary.[42] On the other hand, accelerometer-measured data reveal that older adults spend an average of 9.4 hours/day, or 65-80% of their waking day, sedentary.[42] Accordingly, the use of accelerometer-measured sedentary time in studies among older adults is important when studying associations of this risk factor with different phenotypes.

## The Women's Health Initiative Study Design

### Clinical Trial and Observational Study Components

The Women's Health Initiative (WHI) is a longitudinal study investigating major determinants of chronic diseases in postmenopausal women. The WHI study design has been previously described in great detail.[43,44] Briefly, 161,808 postmenopausal women aged 50 -79 years old were enrolled during 1993-1998. The WHI enrolled women at 40 clinical centers across the nation and included two components: 1) a multifaceted clinical trial (CT) program among 68,132 women and 2) a prospective observational study (OS) among 93,676 women. The CT component included a hormone therapy (HT) trial (n=27,347), a dietary modification (DM) trial to reduce total dietary fat (n=48,835), and a calcium plus vitamin D (CaD) supplementation trial (n=36,282). Women were eligible to enroll in one, two, or all three trials. The HT trial included two components: 1) Women with a history of hysterectomy were randomized to receive estrogen alone or placebo; and 2) Women with an intact uterus were randomized to receive estrogen plus progestin or placebo. Women who were ineligible for or not willing to participate in the CT component were able to enroll in the OS.

Women completed screening and enrollment questionnaires by interview and self-report. Baseline personal information, medical history, medication use, and health-related behaviors were evaluated. Women also underwent a physical examination and provided blood specimens, anthropometric measurements, and blood pressure measurements. At baseline, disease status was self-reported. During study follow-up, disease surveillance occurred biannually for CT participants and annually for OS participants. Incident disease

(except diabetes) was physician-adjudicated by medical record review during study follow-up.[45]

Both of the HT trials were terminated early in 2002 and 2004 for the estrogen plus progestin and estrogen alone trials, respectively. The DM and CaD trials ended in 2005 as originally planned.

Extension Studies

In 2005, women in the CT and OS were asked to join the WHI Extension Study (ES) I for five additional years of follow-up (2005-2010); 115,406 women, or 77% of those who were eligible, re-consented to participate in this study. The ES I included ascertainment of health outcomes (e.g., incident CHD), which were confirmed by trained physician adjudicators. In 2010, a second WHI ES began for an additional five-years of follow-up (2010-2015); 93,500 women (87% of those eligible) from the first ES agreed to participate. Over 30% of women in this study are older than 80 years of age. Only health events in African-Americans, Hispanics, or former HT trial participants are adjudicated in this study, leading to two cohorts: a Medical Records Cohort (MRC) with adjudicated outcome data and a Self-Report Cohort with self-reported outcome data.

Long Life Study (LLS)

During 2012-2013, 7,875 women aged 63 years or older from the WHI Extension II MRC participated in the WHI Long Life Study (LLS). The LLS included a one-time in-person visit either at the participant's home or in the clinic. The LLS exam included: physical measurements (pulse, blood pressure, height, weight, and waist circumference), functional measurements (grip strength, balance, 4-meter timed walk, and chair stand), and a blood draw. Participants selected for the LLS were previously included in GWAS

and cardiovascular disease biomarker studies, and belong to the MRC; therefore, all outcome data are adjudicated. The LLS included white women from the HT trials, and African-American and Hispanic women from both the OS and CT components.

Objective Physical Activity and Cardiovascular Health (OPACH) Study

The LLS also included an ancillary study, Objective Physical Activity and Cardiovascular Health (OPACH). The goals of OPACH were to increase understanding of the health of aging women, with an emphasis on the association of physical activity with cardiovascular events and total mortality. OPACH collected most of its data as part of the LLS exam. As part of the OPACH study, women were also administered a questionnaire assessing physical activity and sedentary behavior. Women were instructed to wear an accelerometer during waking hours (except during swimming or bathing) for a period of seven days to objectively measure sedentary time and various intensity levels of physical activity.

**Objectives**

This dissertation was conducted among participants from the WHI and had three objectives:

1. Determine whether ages at menarche and menopause and reproductive lifespan were associated with survival to age 90, termed "exceptional longevity."
2. Determine whether genetic factors associated with longevity in prior investigations were associated with survival to ages 85 and 90 and healthy aging in white, African-American, and Hispanic women.
3. Determine whether accelerometer-measured and self-reported sedentary time were associated with LTL among older women.

Findings from this dissertation are important in increasing our understanding of determinants and potential mechanisms associated with exceptional survival and cellular aging among postmenopausal women, a rapidly aging population.

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# CHAPTER 2: AGES AT MENARCHE AND MENOPAUSE AND REPRODUCTIVE LIFESPAN AS PREDICTORS OF EXCEPTIONAL LONGEVITY IN WOMEN: THE WOMEN'S HEALTH INITIATIVE

**Abstract**

**Background**: Our objective was to investigate associations between reproductive factors and survival to age 90 years.

**Methods**: Prospective study of postmenopausal women from the Women's Health Initiative recruited from 1993-1998 and followed until the last outcomes evaluation on August 29, 2014. Participants included 16,251 women born on or before August 29, 2014 for whom survival to age 90 during follow-up was ascertained. Women were classified as having survived to age 90 (exceptional longevity) or died before age 90. Multivariable logistic regression models were used to evaluate associations of ages at menarche and menopause (natural or surgical) and reproductive lifespan with longevity, adjusting for demographic, lifestyle, and reproductive characteristics.

**Results**: Participants were on average aged 74.7 years (range, 69-81 years) at baseline. Of 16,251 women, 8,892 (55%) survived to age 90. Women aged ≥12 years at menarche had modestly increased odds of longevity (odds ratio [OR], 1.09; 95% confidence interval [CI], 1.00-1.19). There was a significant trend toward increased longevity for later age at menopause (natural or surgical; $P_{trend}$=0.01), with ORs (95% CIs) of 1.19 (1.04-1.36) and 1.18 (1.02-1.36) for 50-54 and ≥55 compared with <40 years, respectively. Later age at natural menopause as a separate exposure was also significantly associated with longevity ($P_{trend}$=0.02). Longer reproductive lifespan was significantly associated with increased longevity ($P_{trend}$=0.008). The odds of longevity were 13% (OR, 1.13; 95% CI, 1.03-1.25) higher in women with >40 compared with <33 reproductive years.

**Conclusions**: Reproductive characteristics were associated with late-age survival in older women.

## Introduction

The number of women aged 90 years or older in the United States has increased dramatically in the past century. Currently estimated at 1.3 million, this demographic is expected to quadruple by 2050.[1] Despite this rapid increase, exceptional longevity is still considered a rare phenomenon.[2] Factors predisposing to a long lifespan in women are not fully understood.

Although ages at menarche and menopause have been studied in relation to cardiovascular disease, diabetes, and mortality in previous reports,[3-26] their association with longevity has received little attention. Later ages at menarche and menopause have been associated with reduced all-cause and cardiovascular mortality risk in some[4-6,9,13] but not all[7,8,11] studies. Longer reproductive lifespan, defined as the time interval between menarche and menopause, has also been associated with decreased morbidity and mortality.[26-28] These findings suggest that later age at menopause and longer reproductive lifespan may increase the likelihood of long-term survival. However, as prior studies were largely focused on mortality, no study to date has evaluated the association of reproductive factors with survival to a specific advanced age such as 90 years.

We investigated the associations of ages at menarche and menopause and reproductive lifespan with survival to age 90 years in a large, ethnically diverse cohort of postmenopausal women from the Women's Health Initiative (WHI). We also determined whether associations varied by race/ethnicity, baseline smoking behavior, or use of hormone therapy (HT).

## Methods

### Study Population

The WHI is a large, prospective study investigating major determinants of chronic diseases in postmenopausal women. Details of the study have been previously described.[29,30] Briefly, a racially and ethnically diverse cohort of postmenopausal women aged 50 to 79 years old was recruited from 40 clinical centers across the United States between 1993 and 1998. A total of 68,133 women were randomized into one or more of three clinical trials (CT), including one of two HT trials, and 93,676 were enrolled in an observational study (OS). In 2005, 76.9% of 150,075 eligible women consented to further follow-up for an additional five years in the Extension Study (ES), and in 2010, 86.8% of 107,706 women consented for another five years of follow-up. All participants provided written informed consent, and Institutional Review Board approval was received by all participating institutions.

The present study was restricted to CT, OS, and ES participants born on or before August 29, 1924, that is, who had potential to survive to age 90 years during follow-up ending August 29, 2014. Only those with complete information on ages at menarche and menopause whose survival status could be ascertained were included, resulting in a cohort of 16,251 women aged 69 to 81 years at baseline with up to 21 years of follow-up (Figure 2.1).

### Data Collection and Study Variables

At baseline, participants completed self-administered questionnaires assessing demographic characteristics, medical history, reproductive history, and lifestyle behaviors. Age at menarche was defined as age at first menstrual period and categorized

into <12 (early menarche) or ≥12 (average or late menarche) years.[3,7] Age at natural menopause was defined as the age at which a woman last had any menstrual bleeding among those without a self-reported history of hysterectomy or bilateral oophorectomy before age at last menstrual bleeding. Women whose age at natural menopause was >60 years were considered to have experienced menopause at age 60 years. Age at surgical menopause was defined as age at bilateral oophorectomy among those who reported having this procedure performed before age at last menstrual bleeding. A separate variable representing age at natural or surgical menopause combined was also created. Age at menopause was classified into the following categories: <40, 40-44, 45-49, 50-54, or ≥55 years.[14,15,19] Reproductive lifespan was defined as the difference between ages at menopause (natural or surgical) and menarche and categorized into quartiles (<33, 33-37, 38-40, or >40 years). Parity was defined as the number of term pregnancies. Information on past oral contraceptive (OC) use was also collected. HT use was defined according to self-reported use and participation in the HT trials as part of the CT.

Additional covariates collected at baseline included race/ethnicity, marital status, education, smoking, alcohol consumption, and self-rated health. Race/ethnicity was self-selected as American Indian/Alaskan Native, Asian/Pacific Islander, black/African-American, Hispanic/Latina, white, or other. Physical activity was summarized into metabolic equivalents (MET)/week based on the duration, frequency, and intensity of walking and other recreational activities.[31] Trained clinic staff measured height and weight at baseline. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, and categorized according to standard cutpoints.[32]

A history of major age-related diseases was defined as occurrence of one or more of the following diseases, each of which greatly increases a woman's risk of morbidity and mortality: coronary heart disease, cerebrovascular disease, cancer (excluding non-melanoma skin cancer), diabetes, and hip fracture. Disease status was self-reported at baseline, and incident diseases were identified via periodic clinic visits and mailed questionnaires conducted biannually for CT participants through 2005, annually for OS participants, and then annually by mail for all ES participants. Incident diseases except for diabetes were adjudicated by physician medical record review.[33] Diabetes was defined as self-reported physician diagnosis of diabetes treated with oral medication or insulin.[34]

Study Outcome

Women were classified as having survived to age 90 years (exceptional longevity) or died before age 90 years. Death was confirmed by trained physician adjudicators based on hospital records, autopsy or coroner's reports, or death certificates. Periodic linkage to the National Death Index was performed for all participants, including those lost to follow-up. Survival status was ascertained for 82% of participants born on or before August 29, 1924.

Statistical Analysis

Comparisons of baseline characteristics across categories of ages at menarche and menopause and survival were performed using $\chi^2$ tests for categorical variables. Categories of age at menarche and survival were compared using two-sample t-tests or Wilcoxon rank-sum tests for normally distributed and non-normally distributed continuous variables, respectively. Analysis of variance or Kruskal-Wallis tests were used for comparisons of continuous variables across menopausal age categories.

Multivariable logistic regression models were used to determine reproductive characteristics associated with longevity, with results reported as odds ratios (ORs) and 95% confidence intervals (CIs). All multivariable models adjusted for potential confounders including baseline age, WHI study membership (CT or OS), race/ethnicity, education, marital status, smoking, alcohol consumption, physical activity, BMI, HT use, past oral contraceptive (OC) use, and parity.[7,9,10,14,19,25] Models for age at menarche were also adjusted for age at menopause (natural or surgical) and vice versa. Models for reproductive lifespan were adjusted for all of these factors except for age at menopause because of multicollinearity. Additional models were adjusted for a history of age-related diseases and self-rated health to determine whether these factors explain associations between reproductive characteristics and longevity. Tests for linear trend were performed by including reproductive variables as continuous predictors in the models. Interactions between reproductive characteristics and race/ethnicity, HT use, and smoking were assessed using likelihood ratio tests. To determine whether age at menopause was associated with longevity irrespective of type (i.e., natural vs. surgical), an interaction between age at menopause and a binary variable indicating whether menopause occurred due to natural or surgical reasons was also tested in the multivariable model. *P*-values were two-tailed and considered nominally statistically significant at $P<0.05$. All analyses were performed using SAS Version 9.3 (SAS Institute Inc., Cary, NC).

**Results**

At baseline, women were on average 74.7 (standard deviation [SD] 2.3) years old (Table 2.1). Average ages at menarche and menopause (natural or surgical) were 12.8

(SD 1.4; range 9-17) and 49.0 (SD 6.4; range 30-60) years, respectively. Women had a mean of 36.1 (SD 6.5; range 13-51) reproductive years. Reproductive lifespan was highly correlated with age at menopause ($r=0.98$; $p<0.001$) but not age at menarche ($r=-0.19$; $p<0.001$).

At baseline, women with later ages at menarche and menopause were more likely to be in very good health and have never smoked, and less likely to be obese or have a history of diabetes (Tables 2.1 and 2.2). Women with later menarche were also less likely to be college graduates or have a history of CHD and more likely to have later age at menopause and higher parity. Women with later age at menopause were more likely to be married or living as married, be college graduates, report higher levels of physical activity, have a history of past OC use, and have higher parity.

Of 16,251 women who met the inclusion criteria for this study, 8,892 (55%) survived to age 90. Average age at death was 83.7 (SD 3.9) years, and the most common causes of death were cardiovascular disease, cerebrovascular disease, and cancer. At baseline, women who lived to 90 years were more likely to report higher levels of physical activity and be older, college graduates, current drinkers, and in excellent or very good health (Table 2.3). Women achieving exceptional longevity were also less likely to smoke, be obese, or have a history of age-related diseases.

The odds of longevity were modestly higher in women with menarche at ≥12 years (adjusted OR, 1.09; 95% CI, 1.00-1.19) than <12 years (Table 2.4). There was a significant linear trend toward increased longevity for later age at natural or surgical menopause ($P_{trend}=0.01$), with adjusted ORs (95% CIs) of 1.19 (1.04-1.36) and 1.18 (1.02-1.36) for 50-54 and ≥55 compared with <40 years, respectively. There was no

significant interaction between age at menopause and natural vs. surgical menopause in the multivariable model (data not shown). In a separate model, later age at natural menopause was significantly associated with increased longevity ($P_{trend}$=0.02).

There was a significant association of reproductive lifespan with longevity ($P_{trend}$=0.008). Compared with women with <33 reproductive years, the odds of longevity were elevated across all other quartiles of reproductive lifespan. When defining reproductive lifespan as the difference between ages at natural menopause and menarche, findings were similar ($P_{trend}$=0.01; adjusted OR 1.09 [95% CI 0.99-1.20]; OR 1.17 [95% CI 1.06-1.29]; and OR 1.12 [95% CI 1.02-1.24] for 33-37, 38-40, and >40 compared with <33 years.

Findings for age at menarche were no longer significant after adjustment for a history of age-related diseases (and specifically, CHD) and self-rated health. Findings for age at menopause (natural or surgical) were no longer significant after adjustment for self-rated health, but persisted after adjustment for age-related diseases. Findings for reproductive lifespan were similar after additional adjustment for these factors. No interactions between reproductive factors and race/ethnicity, smoking, or HT use were observed (data not shown).

**Discussion**

In this large, prospective study in a racially and ethnically diverse cohort of postmenopausal women with up to 21 years of follow-up, survival to age 90 years was significantly higher in women with later menarche and menopause. Additionally, longer reproductive lifespan was significantly associated with survival to age 90 years. Findings

were independent of demographic characteristics, lifestyle behaviors, BMI, reproductive factors, past OC use, and HT use.

Some studies have observed decreased risk of all-cause and cardiovascular mortality at older menarcheal ages.[3-6,22] In a meta-analysis, each one-year increase in age at menarche was associated with a 3% lower risk of all-cause mortality.[3] Another study observed that the association of later menarche with lower mortality was attenuated in women older than 80 years, suggesting that age at menarche may become less important over time as a risk factor for survival.[5] Concordantly, we observed a modest increase in survival to age 90 years associated with an average or later age at menarche.

We found that later age at menopause overall, age at natural menopause as a separate exposure, and longer reproductive lifespan were associated with increased odds of longevity. Age at natural menopause has been associated with mortality in some[10,14,16] but not all[25] studies. The association of age at surgical menopause with mortality has been inconsistent across studies.[16,17,19,20,24,25] A prior study among white women observed reduced mortality with increased (i.e., ≥40) reproductive years.[28]

Inconsistent associations of age at menopause with mortality may be due to varying definitions of age at menopause, an important consideration when interpreting associations of this reproductive factor with health outcomes. Previous studies used varying methods to determine age at natural or surgical menopause, making direct comparisons with our results difficult.[14,17-20] For example, some studies determined age at menopause by asking whether menstruation stopped due to natural or surgical reasons, without querying history of hysterectomy or bilateral oophorectomy;[17,20] thus, misclassification may have biased findings. Our definition of age at menopause was

comprehensive by taking into account age at final menstrual period, hysterectomy, and bilateral oophorectomy. However, few studies have examined age at menopause as a variable including both natural and surgical menopause.[19,24] A study in >12,000 Dutch women observed a 2% reduction in mortality risk for every one-year increase in age at menopause occurring naturally or surgically, and life expectancy was two years longer among women aged ≥55 compared with <40 years at menopause.[19] It is also possible that the association of later age at menopause with longevity may be partly explained by lower odds of survival due to comorbidities and adverse health status among women who experienced premature menopause, irrespective of the cause.[35]

Several mechanisms may explain the association of reproductive characteristics with longevity. Early menarche has been associated with increased risk of adult obesity, diabetes, and CVD.[9,12,36,37] Later age at menopause and longer reproductive lifespan have been associated with decreased CVD risk, suggesting that prolonged endogenous estrogen exposure may be cardioprotective[23,27,38], or conversely, that factors such as smoking that may damage the ovary causing earlier menopause also damage the cardiovascular system.[39,40] Although our findings persisted after adjustment for BMI and diabetes, age at menarche was no longer significant after adjustment for CHD and self-rated health, and age at menopause was no longer significant after adjustment for self-rated health. We did observe that women with later age at menarche were less likely to have a history of CHD and those with later age at menopause were more likely to be in excellent health at baseline, suggesting a possible explanation for our findings.

Reproductive events, such as menarche, menopause, and pregnancy, may simply be indicators of underlying health status. For example, hypertension of pregnancy and

gestational diabetes, which typically resolve after delivery, may be harbingers of later type 2 diabetes and cardiovascular disease that were unmasked by pregnancy.[41,42] In-utero exposures and childhood exposures (e.g., obesity) may also play a role in reproductive health status.[43,44] Genetic factors have been associated with age at menarche, ages at natural and surgical menopause, and longevity[45-48], suggesting that a common set of genetic factors may explain the link between these reproductive factors and longevity. For example, a genome-wide association study of age at natural menopause identified genetic variants involved in DNA replication and repair pathways, which are pathways central to aging.[46] Specifically, the DNA repair gene exonuclease 1 (*EXO1*) was significantly associated with age at menopause and has been previously associated with increased life expectancy among female centenarians.[49]

This study had several limitations. Women who participated in the WHI may have been healthier at baseline than the general population of postmenopausal women. Furthermore, women who enrolled for additional follow-up were more likely to be white, educated, and healthier at baseline than those who withdrew, thus our findings may be biased by selective attrition. This may explain the large number of exceptional survivors in our cohort. Ages at menarche and menopause were reliant on self-reported data and subject to recall bias. However, a previous study showed recall of age at menarche to be highly reproducible.[50] Age at menopause has been shown to be reproducible but more variable with increasing years since menopause.[51] However, any misclassification of age at menopause is likely to be non-differential, given that survivors and non-survivors had similar average baseline age.

Strengths of this study include the prospective design with 21 years of follow-up, high retention of study participants over time, adjudicated outcome ascertainment, and large, multi-ethnic sample of postmenopausal women who reached nonagenarian status. This study included a cohort of women with a narrow age range, thus limiting potential bias due to birth cohort effects.

In conclusion, average or later age at menarche, later age at menopause, and longer reproductive lifespan were associated with higher likelihood of survival to age 90 years among postmenopausal women. Further studies are needed to elucidate lifestyle, genetic, and environmental factors associated with ages at menarche and menopause and reproductive lifespan to determine potential mechanisms explaining the link between reproductive factors and longevity. With secular trends showing decreasing age at menarche, increasing age at menopause, and a concurrent rise in longevity,[2,52,53] additional studies in younger birth cohorts will be needed to precisely define the relationship between the timing of reproductive events and a woman's length of life.

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Chapter 2, in full, has been submitted for publication of the material as it may appear in *Journal of the American Medical Association*. Shadyab, Aladdin H.; Macera, Caroline A.; Shaffer, Richard A.; Jain, Sonia; Gallo, Linda C.; Gass, Margery L.S.; Waring, Molly E.; Stefanick, Marcia L.; LaCroix, Andrea Z. The dissertation author was the primary investigator and author of this paper.

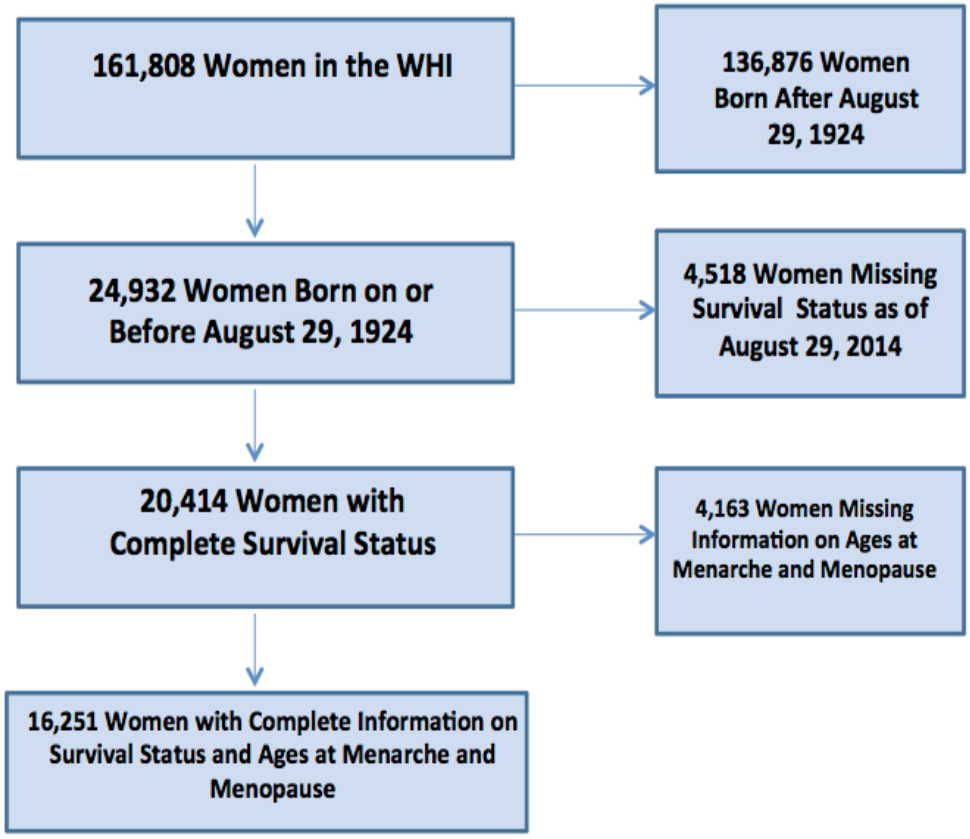


Figure 2.1: Derivation of Final Analytic Sample

Table 2.1: Baseline Characteristics of Postmenopausal Women by Age at Menarche

| | Total Sample | Age at menarche, y | | *P* value |
|---|---|---|---|---|
| | | <12 | ≥12 | |
| Age, mean (SD), y | 74.7 (2.3) | 74.6 (2.3) | 74.7 (2.3) | 0.06 |
| Race/ethnicity | (n=16191) | (n=2696) | (n=13495) | 0.13 |
| White | 14468 (89.4) | 2400 (89.0) | 12068 (89.4) | |
| Black | 856 (5.3) | 155 (5.8) | 701 (5.2) | |
| Hispanic | 222 (1.4) | 46 (1.7) | 176 (1.3) | |
| Other | 645 (4.0) | 95 (3.5) | 550 (4.1) | |
| Educational level | (n=16155) | (n=2694) | (n=13461) | <0.001 |
| Less than high school | 1085 (6.7) | 171 (6.4) | 914 (6.8) | |
| High school | 2807 (17.4) | 420 (15.6) | 2387 (17.7) | |
| Some college | 6425 (39.8) | 1012 (37.6) | 5413 (40.2) | |
| College graduate | 5838 (36.1) | 1091 (40.5) | 4747 (35.3) | |
| Marital status | (n=16183) | (n=2693) | (n=13490) | 0.34 |
| Married/living as married | 7474 (46.2) | 1216 (45.2) | 6258 (46.4) | |
| Widowed | 6372 (39.4) | 1064 (39.5) | 5308 (39.4) | |
| Divorced/separated | 1552 (9.6) | 282 (10.5) | 1270 (9.4) | |
| Never married | 785 (4.9) | 131 (4.9) | 654 (4.9) | |
| Smoking behavior | (n=15968) | (n=2657) | (n=13311) | <0.001 |
| Never smoked | 8919 (55.9) | 1386 (52.2) | 7533 (56.6) | |
| Past smoker | 6415 (40.2) | 1147 (43.2) | 5268 (39.6) | |
| Current smoker | 634 (4.0) | 124 (4.7) | 510 (3.8) | |
| Alcohol intake | (n=16126) | (n=2680) | (n=13446) | 0.08 |
| Nondrinker | 2162 (13.4) | 325 (12.1) | 1837 (13.7) | |
| Past drinker | 3256 (20.2) | 563 (21.0) | 2693 (20.0) | |
| Current drinker | 10708 (66.4) | 1792 (66.9) | 8916 (66.3) | |
| Recreational physical activity, mean (SD), MET-hours/week | 12.1 (13.1) | 11.9 (13.2) | 12.2 (13.1) | 0.14 |
| Body mass index, kg/m$^2$ | (n=16074) | (n=2676) | (n=13398) | <0.001 |
| Underweight (<18.5) | 245 (1.5) | 32 (1.2) | 213 (1.6) | |
| Normal weight (18.5-24.9) | 6238 (38.8) | 838 (31.3) | 5400 (40.3) | |
| Overweight (25.0-29.9) | 5910 (36.8) | 994 (37.1) | 4916 (36.7) | |
| Obese (≥30) | 3681 (22.9) | 812 (30.3) | 2869 (21.4) | |
| History of major age-related diseases[a] | (n=16251) | (n=2708) | (n=13543) | |
| Coronary heart disease | 2325 (14.3) | 430 (15.9) | 1895 (14.0) | 0.01 |
| Stroke | 1772 (10.9) | 292 (10.8) | 1480 (10.9) | 0.82 |
| Cancer (excluding non-melanoma skin cancer) | 4861 (29.9) | 821 (30.3) | 4040 (29.8) | 0.61 |

Abbreviations: HT, hormone therapy; MET, metabolic equivalent; SD, standard deviation; y, years
Data are presented as No. (%) unless otherwise indicated
[a]Includes baseline self-reported and incident adjudicated diseases

Table 2.1: Baseline Characteristics of Postmenopausal Women by Age at Menarche, Continued

| | Total Sample | Age at menarche, y | | *P* value |
|---|---|---|---|---|
| | | <12 | ≥12 | |
| Diabetes | 2266 (13.9) | 442 (16.3) | 1824 (13.5) | <0.001 |
| Hip fracture | 1430 (8.8) | 244 (9.0) | 1186 (8.8) | 0.67 |
| ≥1 disease | 9335 (57.4) | 1617 (59.7) | 7718 (57.0) | 0.009 |
| Self-rated health | (n=16138) | (n=2684) | (n=13454) | 0.02 |
| Excellent | 2059 (12.8) | 340 (12.7) | 1719 (12.8) | |
| Very good | 6327 (39.2) | 1004 (37.4) | 5323 (39.6) | |
| Good | 5971 (37.0) | 1003 (37.4) | 4968 (36.9) | |
| Fair/poor | 1781 (11.0) | 337 (12.6) | 1444 (10.7) | |
| Self-reported HT use | (n=16038) | (n=2673) | (n=13365) | 0.07 |
| Never | 6522 (40.7) | 1033 (38.7) | 5489 (41.1) | |
| Past | 5202 (32.4) | 896 (33.5) | 4306 (32.2) | |
| Current | 4314 (26.9) | 744 (27.8) | 3570 (26.7) | |
| Past oral contraceptive use | (n=16251) 2049 (12.6) | (n=2708) 349 (12.9) | (n=13543) 1700 (12.6) | 0.63 |
| Age at menarche, mean (SD), y | 12.8 (1.4) | | | |
| Age at menopause, mean (SD), y | 49.0 (6.4) | 48.5 (6.8) | 49.0 (6.3) | <0.001 |
| Age at natural menopause, mean (SD), y | 49.2 (6.2) | 48.8 (6.6) | 49.3 (6.2) | 0.004 |
| Age at surgical menopause, mean (SD), y | 45.5 (7.8) | 45.3 (8.2) | 45.6 (7.7) | 0.86 |
| Reproductive lifespan, mean (SD), y | 36.1 (6.5) | 37.8 (6.8) | 35.8 (6.4) | <0.001 |
| Parity | (n=16174) | (n=2697) | (n=13477) | 0.03 |
| Nulliparous | 2165 (13.4) | 395 (14.7) | 1770 (13.1) | |
| 1 | 1502 (9.3) | 273 (10.1) | 1229 (9.1) | |
| 2 | 3907 (24.2) | 665 (24.7) | 3242 (24.1) | |
| 3 | 3747 (23.2) | 602 (22.3) | 3145 (23.3) | |
| 4 | 2436 (15.1) | 396 (14.7) | 2040 (15.1) | |
| ≥5 | 2417 (14.9) | 366 (13.6) | 2051 (15.2) | |

Abbreviations: HT, hormone therapy; MET, metabolic equivalent; SD, standard deviation; y, years
Data are presented as No. (%) unless otherwise indicated
[a]Includes baseline self-reported and incident adjudicated diseases

Table 2.2: Baseline Characteristics of Postmenopausal Women by Age at Menopause

| | Age at menopause, y | | | | | |
|---|---|---|---|---|---|---|
| | <40 | 40-44 | 45-49 | 50-54 | ≥55 | *P* value |
| Age, mean (SD), y | 74.6 (2.3) | 74.7 (2.3) | 74.7 (2.3) | 74.7 (2.2) | 74.7 (2.3) | 0.17 |
| Race/ethnicity | (n=1247) | (n=2103) | (n=3432) | (n=6312) | (n=3097) | <0.001 |
| White | 1016 (81.5) | 1802 (85.7) | 3133 (90.7) | 5735 (90.9) | 2802 (90.5) | |
| Black | 145 (11.6) | 155 (7.4) | 157 (4.6) | 259 (4.1) | 140 (4.5) | |
| Hispanic | 23 (1.8) | 47 (2.2) | 36 (1.1) | 73 (1.2) | 43 (1.4) | |
| Other | 63 (5.1) | 99 (4.7) | 126 (3.7) | 245 (3.9) | 112 (3.6) | |
| Educational level | (n=1242) | (n=2095) | (n=3418) | (n=6305) | (n=3095) | <0.001 |
| Less than high school | 145 (11.7) | 180 (8.6) | 216 (6.3) | 370 (5.9) | 174 (5.6) | |
| High school | 249 (20.1) | 419 (20.0) | 599 (17.5) | 1082 (17.2) | 458 (14.8) | |
| Some college | 509 (41.0) | 860 (41.1) | 1388 (40.6) | 2465 (39.1) | 1203 (38.9) | |
| College graduate | 339 (27.3) | 636 (30.4) | 1215 (35.6) | 2388 (37.9) | 1260 (40.7) | |
| Marital status | (n=1248) | (n=2093) | (n=3426) | (n=6314) | (n=3102) | <0.001 |
| Married/living as married | 532 (42.6) | 942 (45.0) | 1507 (44.0) | 2970 (47.0) | 1523 (49.1) | |
| Widowed | 538 (43.1) | 848 (40.5) | 1380 (40.3) | 2470 (39.1) | 1136 (36.6) | |
| Divorced/separated | 126 (10.1) | 193 (9.2) | 354 (10.3) | 567 (9.0) | 312 (10.1) | |
| Never married | 52 (4.2) | 110 (5.3) | 185 (5.4) | 307 (4.9) | 131 (4.2) | |
| Smoking behavior | (n=1226) | (n=2066) | (n=3381) | (n=6224) | (n=3071) | 0.04 |
| Never smoked | 678 (55.3) | 1136 (55.0) | 1858 (55.0) | 3480 (55.9) | 1767 (57.5) | |
| Past smoker | 484 (39.5) | 832 (40.3) | 1382 (40.9) | 2517 (40.4) | 1200 (39.1) | |
| Current smoker | 64 (5.2) | 98 (4.7) | 141 (4.2) | 227 (3.7) | 104 (3.4) | |
| Alcohol intake | (n=1240) | (n=2092) | (n=3416) | (n=6288) | (n=3090) | <0.001 |
| Nondrinker | 220 (17.7) | 298 (14.2) | 463 (13.6) | 826 (13.1) | 355 (11.5) | |
| Past drinker | 294 (23.7) | 474 (22.7) | 672 (19.7) | 1203 (19.1) | 613 (19.8) | |
| Current drinker | 726 (58.6) | 1320 (63.1) | 2281 (66.8) | 4259 (67.7) | 2122 (68.7) | |
| Recreational physical activity, mean (SD), MET-hours/week | 11.8 (14.1) | 11.1 (12.2) | 11.5 (12.2) | 12.5 (13.4) | 12.9 (13.3) | <0.001 |

Abbreviations: HT, hormone therapy; MET, metabolic equivalent; SD, standard deviation; y, years
Data are presented as No. (%) unless otherwise indicated
[a]Includes baseline self-reported and incident adjudicated diseases

Table 2.2: Baseline Characteristics of Postmenopausal Women by Age at Menopause, Continued

| | Age at menopause, y | | | | | |
|---|---|---|---|---|---|---|
| | <40 | 40-44 | 45-49 | 50-54 | ≥55 | *P* value |
| Body mass index, kg/m$^2$ | (n=1244) | (n=2083) | (n=3399) | (n=6262) | (n=3086) | <0.001 |
| Underweight (<18.5) | 14 (1.1) | 26 (1.3) | 56 (1.7) | 96 (1.5) | 53 (1.7) | |
| Normal weight (18.5-24.9) | 420 (33.8) | 747 (35.9) | 1309 (38.5) | 2501 (39.9) | 1261 (40.9) | |
| Overweight (25.0-29.9) | 479 (38.5) | 759 (36.4) | 1288 (37.9) | 2309 (36.9) | 1075 (34.8) | |
| Obese (≥30) | 331 (26.6) | 551 (26.5) | 746 (22.0) | 1356 (21.7) | 697 (22.6) | |
| History of major age-related diseases[a] | (n=1251) | (n=2107) | (n=3443) | (n=6335) | (n=3115) | |
| Coronary heart disease | 199 (15.9) | 333 (15.8) | 499 (14.5) | 868 (13.7) | 426 (13.7) | 0.05 |
| Stroke | 148 (11.8) | 227 (10.8) | 370 (10.8) | 693 (10.9) | 334 (10.7) | 0.85 |
| Cancer (excluding non-melanoma skin cancer) | 360 (28.8) | 648 (30.8) | 991 (28.8) | 1878 (29.6) | 984 (31.6) | 0.09 |
| Diabetes | 206 (16.5) | 321 (15.2) | 475 (13.8) | 835 (13.2) | 429 (13.8) | 0.01 |
| Hip fracture | 107 (8.6) | 182 (8.6) | 317 (9.2) | 532 (8.4) | 292 (9.4) | 0.49 |
| ≥1 disease | 738 (59.0) | 1236 (58.7) | 1956 (56.8) | 3583 (56.6) | 1822 (58.5) | 0.16 |
| Self-rated health | (n=1240) | (n=2090) | (n=3418) | (n=6293) | (n=3097) | <0.001 |
| Excellent | 115 (9.3) | 236 (11.3) | 431 (12.6) | 815 (13.0) | 462 (14.9) | |
| Very good | 420 (33.9) | 784 (37.5) | 1317 (38.5) | 2567 (40.8) | 1239 (40.0) | |
| Good | 499 (40.2) | 807 (38.6) | 1298 (38.0) | 2275 (36.2) | 1092 (35.3) | |
| Fair/poor | 206 (16.6) | 263 (12.6) | 372 (10.9) | 636 (10.1) | 304 (9.8) | |
| Self-reported HT use | (n=1235) | (n=2082) | (n=3393) | (n=6250) | (n=3078) | <0.001 |
| Never | 410 (33.2) | 780 (37.5) | 1398 (41.2) | 2776 (44.4) | 1158 (37.6) | |
| Past | 401 (32.5) | 695 (33.4) | 1143 (33.7) | 2001 (32.0) | 962 (31.3) | |
| Current | 424 (34.3) | 607 (29.2) | 852 (25.1) | 1473 (23.6) | 958 (31.1) | |
| | (n=1251) | (n=2107) | (n=3443) | (n=6335) | (n=3115) | |
| Past oral contraceptive use | 32 (2.6) | 149 (7.1) | 418 (12.1) | 940 (14.8) | 510 (16.4) | <0.001 |
| Age at menarche, mean (SD), y | 12.7 (1.6) | 12.8 (1.5) | 12.9 (1.4) | 12.8 (1.4) | 12.9 (1.5) | <0.001 |
| Reproductive lifespan, mean (SD), y | 22.2 (3.2) | 28.8 (2.0) | 33.9 (2.0) | 38.5 (2.0) | 44.3 (2.7) | <0.001 |

Abbreviations: HT, hormone therapy; MET, metabolic equivalent; SD, standard deviation; y, years
Data are presented as No. (%) unless otherwise indicated
[a]Includes baseline self-reported and incident adjudicated disease

Table 2.2: Baseline Characteristics of Postmenopausal Women by Age at Menopause, Continued

| | Age at menopause, y | | | | | |
|---|---|---|---|---|---|---|
| | <40 | 40-44 | 45-49 | 50-54 | ≥55 | *P* value |
| Parity | (n=1246) | (n=2094) | (n=3430) | (n=6298) | (n=3106) | <0.001 |
| Nulliparous | 254 (20.4) | 332 (15.9) | 481 (14.0) | 765 (12.2) | 333 (10.7) | |
| 1 | 146 (11.7) | 228 (10.9) | 332 (9.7) | 536 (8.5) | 260 (8.4) | |
| 2 | 311 (25.0) | 474 (22.6) | 825 (24.1) | 1525 (24.2) | 772 (24.9) | |
| 3 | 231 (18.5) | 462 (22.1) | 806 (23.5) | 1495 (23.7) | 753 (24.2) | |
| 4 | 150 (12.0) | 281 (13.4) | 500 (14.6) | 997 (15.8) | 508 (16.4) | |
| ≥5 | 154 (12.4) | 317 (15.1) | 486 (14.2) | 980 (15.6) | 480 (15.5) | |

Abbreviations: HT, hormone therapy; MET, metabolic equivalent; SD, standard deviation; y, years
Data are presented as No. (%) unless otherwise indicated
[a]Includes baseline self-reported and incident adjudicated diseases

Table 2.3: Baseline Characteristics of Postmenopausal Women in Relation to Survival to Age 90 Years

| Characteristic | Survived to age 90 (n=8892) | Died before age 90 (n=7359) | *P* value |
|---|---|---|---|
| Age, mean (SD), y | 75.1 (2.2) | 74.2 (2.3) | <0.001 |
| Race/ethnicity | (n=8859) | (n=7332) | |
| White | 7936 (89.6) | 6532 (89.1) | |
| Black | 430 (4.9) | 426 (5.8) | 0.008 |
| Hispanic | 115 (1.3) | 107 (1.5) | |
| Other | 378 (4.3) | 267 (3.6) | |
| Educational level | (n=8849) | (n=7306) | |
| Less than high school | 528 (6.0) | 557 (7.6) | |
| High school | 1482 (16.8) | 1325 (18.1) | <0.001 |
| Some college | 3503 (39.6) | 2922 (40.0) | |
| College graduate | 3336 (37.7) | 2502 (34.3) | |
| Marital status | (n=8860) | (n=7323) | |
| Married/living as married | 4267 (48.2) | 3207 (43.8) | |
| Widowed | 3417 (38.6) | 2955 (40.4) | <0.001 |
| Divorced/separated | 759 (8.6) | 793 (10.8) | |
| Never married | 417 (4.7) | 368 (5.0) | |
| Smoking behavior | (n=8762) | (n=7206) | |
| Never smoked | 5276 (60.2) | 3643 (50.6) | |
| Past smoker | 3317 (37.9) | 3098 (43.0) | <0.001 |
| Current smoker | 169 (1.9) | 465 (6.5) | |
| Alcohol intake | (n=8832) | (n=7294) | |
| Nondrinker | 1184 (13.4) | 978 (13.4) | |
| Past drinker | 1560 (17.7) | 1696 (23.3) | <0.001 |
| Current drinker | 6088 (68.9) | 4620 (63.3) | |
| Recreational physical activity, mean (SD), MET-hours/week | 12.9 (13.4) | 11.2 (12.6) | <0.001 |
| Body mass index, kg/m$^2$ | (n=8797) | (n=7277) | |
| Underweight (<18.5) | 104 (1.2) | 141 (1.9) | |
| Normal weight (18.5-24.9) | 3518 (40.0) | 2720 (37.4) | <0.001 |
| Overweight (25.0-29.9) | 3348 (38.1) | 2562 (35.2) | |
| Obese (≥30) | 1827 (20.8) | 1854 (25.5) | |
| History of major age-related diseases[a] | (n=8892) | (n=7359) | |
| Coronary heart disease | 719 (8.1) | 1606 (21.8) | <0.001 |
| Stroke | 542 (6.1) | 1230 (16.7) | <0.001 |

Abbreviations: HT, hormone therapy; MET, metabolic equivalents; SD, standard deviation
Data are presented as No. (%) unless otherwise indicated
[a]Includes baseline self-reported and incident adjudicated diseases
[b]Includes HT use based on self-report and due to participation in HT trials

Table 2.3: Baseline Characteristics of Postmenopausal Women in Relation to Survival to Age 90 Years, Continued

| Characteristic | Survived to age 90 (n=8892) | Died before age 90 (n=7359) | *P* value |
|---|---|---|---|
| Cancer (excluding non-melanoma skin cancer) | 2021 (22.7) | 2840 (38.6) | <0.001 |
| Diabetes | 1078 (12.1) | 1188 (16.1) | <0.001 |
| Hip fracture | 704 (7.9) | 726 (9.9) | <0.001 |
| ≥1 disease | 4022 (45.2) | 5313 (72.2) | <0.001 |
| | | | |
| Self-rated health | (n=8838) | (n=7300) | |
| Excellent | 1339 (15.2) | 720 (9.9) | |
| Very good | 3786 (42.8) | 2541 (34.8) | <0.001 |
| Good | 3063 (34.7) | 2908 (39.8) | |
| Fair/poor | 650 (7.4) | 1131 (15.5) | |
| | | | |
| | (n=8773) | (n=7265) | |
| Ever HT use[b] | 5646 (64.4) | 4546 (62.6) | 0.02 |
| | | | |
| | (n=8892) | (n=7359) | |
| Past oral contraceptive use | 1115 (12.5) | 934 (12.7) | 0.77 |
| | | | |
| Age at menarche, y | (n=8892) | (n=7359) | |
| <12 | 1415 (15.9) | 1293 (17.6) | 0.005 |
| ≥12 | 7477 (84.1) | 6066 (82.4) | |
| | | | |
| Age at menopause, y | (n=8892) | (n=7359) | |
| <40 | 609 (6.9) | 642 (8.7) | |
| 40-44 | 1099 (12.4) | 1008 (13.7) | |
| 45-49 | 1878 (21.1) | 1565 (21.3) | <0.001 |
| 50-54 | 3554 (40.0) | 2781 (37.8) | |
| ≥55 | 1752 (19.7) | 1363 (18.5) | |
| | | | |
| Age at natural menopause, y | (n=8336) | (n=6900) | |
| <40 | 494 (5.9) | 515 (7.5) | |
| 40-44 | 995 (11.9) | 915 (13.3) | |
| 45-49 | 1721 (20.7) | 1447 (21.0) | <0.001 |
| 50-54 | 3450 (41.4) | 2709 (39.3) | |
| ≥55 | 1676 (20.1) | 1314 (19.0) | |
| | | | |
| Age at surgical menopause, y | (n=556) | (n=459) | |
| <40 | 115 (20.7) | 127 (27.7) | |
| 40-44 | 104 (18.7) | 93 (20.3) | |
| 45-49 | 157 (28.2) | 118 (25.7) | 0.06 |
| 50-54 | 104 (18.7) | 72 (15.7) | |
| ≥55 | 76 (13.7) | 49 (10.7) | |

Abbreviations: HT, hormone therapy; MET, metabolic equivalents; SD, standard deviation
Data are presented as No. (%) unless otherwise indicated
[a]Includes baseline self-reported and incident adjudicated diseases
[b]Includes HT use based on self-report and due to participation in HT trials

Table 2.3: Baseline Characteristics of Postmenopausal Women in Relation to Survival to Age 90 Years, Continued

| Characteristic | Survived to age 90 (n=8892) | Died before age 90 (n=7359) | *P* value |
|---|---|---|---|
| Reproductive lifespan, y | (n=8892) | (n=7359) | |
| <33 | 2127 (23.9) | 2014 (27.4) | |
| 33-37 | 2499 (28.1) | 2015 (27.4) | <0.001 |
| 38-40 | 2068 (23.3) | 1601 (21.8) | |
| >40 | 2198 (24.7) | 1729 (23.5) | |
| | | | |
| Parity | (n=8849) | (n=7325) | |
| Nulliparous | 1160 (13.1) | 1005 (13.7) | |
| 1 | 764 (8.6) | 738 (10.1) | |
| 2 | 2234 (25.3) | 1673 (22.8) | <0.001 |
| 3 | 2111 (23.9) | 1636 (22.3) | |
| 4 | 1347 (15.2) | 1089 (14.9) | |
| ≥5 | 1233 (13.9) | 1184 (16.2) | |

Abbreviations: HT, hormone therapy; MET, metabolic equivalents; SD, standard deviation
Data are presented as No. (%) unless otherwise indicated
[a]Includes baseline self-reported and incident adjudicated diseases
[b]Includes HT use based on self-report and due to participation in HT trials

Table 2.4: Associations of Reproductive Characteristics with Survival to Age 90 among Postmenopausal Women

| | No./total (%) survived to 90 | Age-adjusted OR (95% CI) | *P* value for trend | Multivariable-adjusted OR (95% CI) | *P* value for trend |
|---|---|---|---|---|---|
| Age at menarche[a], y | | | | | |
| <12 | 1415/2708 (52.3) | 1 [Reference] | 0.61 | 1 [Reference] | 0.77 |
| ≥12 | 7477/13543 (55.2) | 1.11 (1.02-1.21) | | 1.09 (1.00-1.19) | |
| Age at menopause[a], y | | | | | |
| <40 | 609/1251 (48.7) | 1 [Reference] | | 1 [Reference] | |
| 40-44 | 1099/2107 (52.2) | 1.13 (0.98-1.31) | | 1.09 (0.94-1.27) | |
| 45-49 | 1878/3443 (54.6) | 1.24 (1.09-1.41) | <0.001 | 1.13 (0.98-1.30) | 0.01 |
| 50-54 | 3554/6335 (56.1) | 1.32 (1.17-1.50) | | 1.19 (1.04-1.36) | |
| ≥55 | 1752/3115 (56.2) | 1.34 (1.17-1.53) | | 1.18 (1.02-1.36) | |
| Age at natural menopause[a], y | | | | | |
| <40 | 494/1009 (49.0) | 1 [Reference] | | 1 [Reference] | |
| 40-44 | 995/1910 (52.1) | 1.12 (0.96-1.31) | | 1.06 (0.90-1.25) | |
| 45-49 | 1721/3168 (54.3) | 1.22 (1.05-1.41) | <0.001 | 1.11 (0.95-1.29) | 0.02 |
| 50-54 | 3450/6159 (56.0) | 1.31 (1.14-1.50) | | 1.18 (1.02-1.36) | |
| ≥55 | 1676/2990 (56.1) | 1.32 (1.14-1.53) | | 1.16 (0.99-1.36) | |
| Age at surgical menopause[a], y | | | | | |
| <40 | 115/242 (47.5) | 1 [Reference] | | 1 [Reference] | |
| 40-44 | 104/197 (52.8) | 1.23 (0.83-1.82) | | 1.35 (0.88-2.08) | |
| 45-49 | 157/275 (57.1) | 1.46 (1.02-2.09) | 0.02 | 1.33 (0.90-1.98) | 0.11 |
| 50-54 | 104/176 (59.1) | 1.59 (1.06-2.38) | | 1.50 (0.96-2.34) | |
| ≥55 | 76/125 (60.8) | 1.50 (0.96-2.36) | | 1.43 (0.86-2.38) | |
| Reproductive lifespan[b], y | | | | | |
| <33 | 2127/4141 (51.4) | 1 [Reference] | | 1 [Reference] | |
| 33-37 | 2499/4514 (55.4) | 1.17 (1.07-1.27) | | 1.11 (1.01-1.21) | |
| 38-40 | 2068/3669 (56.4) | 1.22 (1.12-1.34) | <0.001 | 1.17 (1.06-1.29) | 0.008 |
| >40 | 2198/3927 (56.0) | 1.21 (1.11-1.33) | | 1.13 (1.03-1.25) | |

Abbreviations: CI, confidence interval; OR, odds ratio; y, years

[a]Multivariable model adjusts for baseline age, study membership (clinical trial or observational study), demographics (race/ethnicity, educational level, baseline marital status), lifestyle behaviors (baseline smoking behavior, baseline alcohol intake, baseline physical activity), baseline body mass index, and reproductive factors (ever using hormone therapy, past oral contraceptive use, age at menopause, age at menarche, and parity)

[b]Multivariable model adjusts for baseline age, study membership (clinical trial or observational study), demographics (race/ethnicity, educational level, baseline marital status), lifestyle behaviors (baseline smoking behavior, baseline alcohol intake, baseline physical activity), baseline body mass index, and reproductive factors (ever using hormone therapy, past oral contraceptive use, age at menarche, and parity)

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# CHAPTER 3: REPLICATION OF GENOME-WIDE ASSOCIATION STUDY FINDINGS OF LONGEVITY IN WHITE, AFRICAN-AMERICAN, AND HISPANIC WOMEN: THE WOMEN'S HEALTH INITIATIVE

**Abstract**

**Background**: In previous candidate gene and genome-wide association studies (GWAS), only variants at or near the *APOE* and *FOXO3A* genes have been consistently associated with longevity. However, no study has evaluated whether these genetic factors are associated with longevity in African-Americans and Hispanics, and it is unclear whether these genetic factors are associated with healthy aging.

**Methods**: In this study, we used data from multiple GWAS to determine whether 14 genetic variants previously associated with longevity in GWAS among European populations (index single nucleotide polymorphisms [SNPs]) were associated with survival to ages 85 and 90 in 11,154 white, African-American, and Hispanic women from the Women's Health Initiative. We also determined whether these variants were associated with healthy aging, defined as survival to age 85 without chronic diseases or disability.

**Results**: Among white women, three index SNPs (rs2075650, rs4420638, and rs429358), all located at or near the *APOE* gene, were significantly associated with survival to age 90 after correction for multiple testing ($p<0.001$); rs4420638 and rs429358 were also significantly associated with healthy aging ($p=0.02$). In African-American women, no SNP was associated with longevity. In Hispanic women, seven SNPs in linkage disequilibrium with rs2149954 (located between the *CLINT1* and *EBF1* genes) were significantly associated with survival to age 85 ($p=0.04$).

**Conclusions**: Findings extend previous observations that variation at *APOE* is associated with long-term survival in white women and suggest that variation at this gene

may be associated with healthy aging. Future studies are needed to identify novel loci associated with longevity in African-American and Hispanic women.

## Introduction

The rate of survival into advanced old age among women has undergone a rapid rise in the past century. By 2060, it is expected that approximately 12 million women will be ages 85 and older, commonly referred to as the "oldest-old" age group.[1] While attaining longevity is becoming increasingly common, healthy aging, or reaching old age free of morbidity and disability, is more important from a public health perspective. However, factors contributing to longevity and healthy aging in women are not completely understood.

Although longevity may be largely influenced by maintaining healthy lifestyle behaviors[2], genetic factors may also be important, with heritability estimates for longevity of 25-30%.[3] In previous candidate gene association studies, only variants at apolipoprotein E (*APOE*) and forkhead box O3A (*FOXO3A*), genes involved in Alzheimer's disease risk and insulin-signaling pathways, respectively, have been consistently associated with longevity.[3-12] Furthermore, in genome-wide association studies (GWAS) and meta-analyses of GWAS, only variants near the *APOE* locus have consistently achieved genome-wide significant associations with longevity.[13-17] For example, in a recent meta-analysis among >6,000 nonagenarians and >3,000 controls who died between ages 55 and 80 years, the single nucleotide polymorphism (SNP) rs2075650, located at the *TOMM40* gene near *APOE*, reached genome-wide significance.[13] However, this study and others included samples consisting only of individuals of European descent, and the association between genetic factors and longevity in minorities, such as African-Americans and Hispanics, has not been explored

to date. Furthermore, it is currently unknown whether genetic factors are associated with healthy aging.

In the current study, we used genetic data obtained from multiple GWAS conducted in the Women's Health Initiative (WHI) to determine whether genetic variants previously associated with longevity in populations of European descent (index SNPs) were associated with survival to ages 85 and 90 and healthy aging in cohorts of postmenopausal white, African-American, and Hispanic women, after adjusting for demographic characteristics, lifestyle behaviors, age-related diseases, and population stratification.

## Methods

### Study Population

The WHI is a large, prospective study investigating major determinants of chronic diseases in postmenopausal women. Details of the study have been previously described.[18,19] Briefly, a racially and ethnically diverse cohort of 161,808 postmenopausal women aged 50-79 years old was recruited from 40 clinical centers across the United States between 1993 and 1998. Women participated in an observational study (OS) or ≥1 clinical trial (CT), including one of two hormone therapy (HT) trials, a calcium and vitamin D supplement trial, and a dietary modification trial. In 2005, 76.9% of 150,075 eligible women consented to further follow-up for an additional five years in the Extension Study (ES), and in 2010, 86.8% of 107,706 women consented for another five years of follow-up. All participants provided written informed consent, and Institutional Review Board approval was received by all participating institutions.

This study included participants from six WHI GWAS: 1) the SNP Health Association Resource (SHARe); 2) the Genomics and Randomized Trials Network (GARNET); 3) the Hip Fracture GWAS (HipFx); 4) the WHI Memory Study (WHIMS); 5) the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO); and 6) Modification of PM-Mediated Arrhythmogenesis in Populations (MOPMAP). SHARe is a cohort study among 12,007 self-identified African-American (n=8,405) and Hispanic-American (n=3,602) women who participated in either the OS or CT. GARNET is a case-control trial of 4,416 European-Americans who participated in the HT with myocardial infarction, stroke, venous thrombosis, diabetes, and matching controls. HipFx is a case-control study among 3,690 mostly European-American women. WHIMS is a cohort study of HT participants investigating the incidence of possible dementia and mild cognitive impairment[20]; GWAS data on 5,687 European-Americans were collected. GECCO is a case-control study on colorectal cancer among 2,493 European-Americans. MOPMAP is a case-control study on ventricular ectopy among 3,069 European-Americans. Some participants were included in more than one of these studies.

This study was exclusive to women with genetic data who were born on or before August 29, 1929 and thus could survive to age 85 during follow-up ending August 29, 2014 (Figure 3.1). Only those whose survival status could be ascertained were included. After quality control procedures, the final sample size included 11,154 women (8,656 white, 1,858 African-American, and 539 Hispanic women).

Genotyping

SHARe. DNA samples plus 2% (n=188) blinded duplicate pairs were sent to Affymetrix Inc. for genotyping on the Genome-wide Human SNP Array 6.0 (909,622

SNPs); ~1% of samples failed genotyping. Samples with a call rate <95%, unexpected duplicates, and genotype data on the Y chromosome were excluded. For 188 pairs of blinded duplicate samples, an average concordance of 99.8% was observed. SNPs with a call rate <95%, concordance for duplicates <98%, a minor allele frequency ≤1%, or a Hardy-Weinberg equilibrium p-value $<10^{-4}$ were excluded.

HipFx. DNA samples were sent for genotyping on the Illumina 550k and 610k SNP arrays. Samples with a call rate <98%, unexpected duplicates, and genotype data on the Y chromosome were excluded. Discordant SNPs and those with a call rate <98%, minor allele frequency ≤1%, or a Hardy-Weinberg equilibrium p-value $<10^{-4}$ were excluded.

GARNET. DNA samples plus 1% (n=35) blinded duplicate pairs were sent to the Broad Institute Genetic Analysis Platform for genotyping on the Illumina HumanOmni1-Quad v1-0 B SNP array (1,016,423 SNPs); ~2.7% of samples failed genotyping. Samples with a call rate <98%, unexpected duplicates, and genotype data on the Y chromosome were excluded. An average concordance of 99.8% was observed for 35 pairs of blinded duplicate samples. SNPs were excluded if they had a call rate <98%, >0 discordant call in duplicate genotyping, >1 sample trio inheritance errors, Beadstudio metrics GenTrain score <0.6 or cluster separation values <0.4, or a Hardy-Weinberg equilibrium p-value $<10^{-4}$.

WHIMS. DNA samples plus 4.8% (n=293) blinded duplicate pairs were sent to the Broad Institute Genetic Analysis Platform for genotyping on the Illumina HumanOmniExpressExome-8 v1.0 SNP array; ~7% failed genotyping. Samples with a call rate <97%, unexpected duplicates, and genotype data on the Y chromosome were

excluded. For 293 pairs of blinded duplicate samples, an average concordance of 99.9% was observed. SNPs with a call rate <98%, concordance for duplicates <99%, a minor allele frequency ≤1%, or a Hardy-Weinberg equilibrium p-value $<10^{-4}$ were excluded.

GECCO. DNA samples were sent for genotyping on the Illumina Human610-Quad v1.0 and Cytochip 370k SNP arrays. Samples with a call rate <97%, unexpected duplicates, and genotype data on the Y chromosome were excluded. For pairs of blinded duplicate samples, an average concordance of 97% was observed. Discordant SNPs and those with a call rate <98%, concordance for duplicates <97%, a minor allele frequency <5%, or a Hardy-Weinberg equilibrium p-value $<10^{-4}$ were excluded.

MOPMAP. DNA samples were sent for genotyping on the Affymetrix Gene Titan and Axiom Genome-Wide Human CEU SNP arrays. Samples with a call rate <95%, unexpected duplicates, and genotype data on the Y chromosome were excluded. SNPs with a call rate <90%, a minor allele frequency ≤0.5%, or a Hardy-Weinberg equilibrium p-value $<10^{-6}$ were excluded.

Imputation

All GWAS were imputed to the 1000 Genomes Project (1kGP). The X chromosome was not imputed. Version v2.20101123 of the 1kGP reference panel was used for GECCO, and version v3.20101123 for the other studies. The 1kGP reference panel consists of 1,092 samples, including 246 Africans, 181 admixed Americans, 286 Asians, and 379 Europeans. The GWAS data were first split into chunks, with each chunk having 10,000 SNPs and neighboring chunks having 1,000 overlapping SNPs. All SNP sets were then phased using BEAGLE.[21] SHARe was imputed to 1kGP using MACH.[22] SNPs that were poorly imputed were excluded (i.e., $r^2$ <0.4). Genotype data

derived from imputation were reported as continuous dosage values between 0 and 2 representing the expected number of copies of an allele at that SNP conditional on the directly observed genotypes in both the subject and the phased haplotype assignments in the 1kGP samples.

Genetic Ancestry

A principal components analysis using a subset of 5,665 SNPs common between our samples and the reference panels was performed to identify participants whose genetic ancestry was inconsistent with their self-reported ethnicity. Eigenvectors were calculated using Eigenstrat.[23] We used 475 publically available samples from four ancestral populations including the Yourbans from Ibadan, Nigera (YRI); Utah residents with Northern and Western European ancestry (CEU); the Human Genome Diversity Project (HGDP) East Asian population; and the HGDP Native American populations.[24,25] Participants whose genetic ancestry was inconsistent with their self-reported ethnicity were excluded from the analysis (n=19).

Relatedness

An identity-by-descent analysis was carried out by using a subset of 5,665 SNPs and the PLINK package to identify parent-offspring pairs and pairs of siblings and first-degree relatives.[26] Only one relative from each relative-pair (n=98) was included in the analyses.

Harmonization

The data from the six GWAS underwent harmonization to create a dataset comprised of genetic data from all studies. A panel of 5,655 SNPs was used to check the pairwise concordance among all samples across studies. Another principal components

analysis was done for combined samples (after removing ineligible duplicates) in all studies, and the resulting principal components were mapped back to the samples within each study. As subjects from these GWAS were selected independently, we checked for duplicates between studies. We removed a small number of samples that were supposed to be duplicates but had a concordance rate <90%, and appeared as duplicates but were from unrelated individuals who appeared not to be monozygotic twins.

Selection of SNPs

SNPs significantly associated with longevity at the genome-wide level ($p<5x10^{-8}$) in previous GWAS, replication of GWAS findings, and meta-analyses of GWAS were selected. The two SNPs that define the three isoforms of *APOE* and SNPs significantly associated with longevity in candidate gene studies for *FOXO3A* were also selected. For candidate gene studies, SNPs were selected if statistically significant after correction for multiple testing (e.g., Bonferroni correction). Henceforth, SNPs selected from previous studies will be referred to as "index SNPs." In total, 14 index SNPs were chosen[8-17]: rs2075650 (*TOMM40*); rs4420638 (*APOC1*); rs7412 and rs429358 (*APOE*); rs2149954 (between *CLINT1* and *EBF1*); and rs10457180, rs2764264, rs13217795, rs2802292, rs9400239, rs3800231, rs479744, rs1935949, and rs4946935 (*FOXO3A*).

The index SNPs selected for this study represent genetic variation in a particular region and are in linkage disequilibrium (LD) with other SNPs, which may include the true functional variant. Individuals from different genetic ancestries exhibit divergent LD patterns. Therefore, index SNPs associated with longevity in prior studies among individuals of European descent may not be in LD with functional variants in African-Americans or Hispanics, and may not replicate in these other populations; there may be

other SNPs in the region in LD with the functional variant. Accordingly, for African-Americans and Hispanics, proxy SNPs in LD with the index SNPs were chosen to fully explore replication of prior GWAS and candidate gene study findings in these groups. Proxy SNPs were selected if in high LD ($r^2 \geq 0.8$) with and located within 500kb of the index SNP. Proxy SNP selection was performed using SNAP, a SNP annotation and proxy search.[27] Among African-Americans, SNPs in LD were determined using the Yoruba in Ibadan, Nigera population from HapMap 2, release 22. Among Hispanics, SNPs in LD were determined using the Mexican population from HapMap 3, release 2 (the majority of Hispanics in the WHI were of Mexican descent). Some index SNPs had no SNPs with $r^2 \geq 0.8$ in these HapMap populations, thus proxy SNPs were not selected. Overall, 28 SNPs in African-Americans and 31 SNPs in Hispanics were analyzed.

Covariates

Baseline covariates that may be associated with longevity were selected, including baseline age, race/ethnicity, marital status, education, smoking, and alcohol consumption. Physical activity was summarized into metabolic equivalents (MET)/week based on the duration, frequency, and intensity of walking and other recreational activities.[28] Trained clinic staff measured height and weight at baseline, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

A history of major age-related diseases was defined as occurrence of one or more of the following diseases, each of which greatly increases a woman's risk of morbidity and mortality: coronary heart disease, cerebrovascular disease, cancer (excluding non-melanoma skin cancer), diabetes, or hip fracture. Disease status was self-reported at baseline, and incident diseases were identified via periodic clinic visits and mailed

questionnaires conducted biannually for CT participants and annually for OS and ES participants. Incident diseases except for diabetes were adjudicated by physician medical record review.[29] Diabetes was defined as self-reported physician diagnosis of diabetes treated with oral medication or insulin.

Study Outcomes

Women were classified as having survived to age 85 or died before this age. Women were also classified as having survived to age 90 or died before this age in a separate outcome. Death was confirmed by trained physician adjudicators based on hospital records, autopsy or coroner's reports, or death certificates. Periodic linkage to the National Death Index was performed for all participants, including those lost to follow-up. Approximately 89% of women eligible for inclusion in this study had complete survival status ascertainment.

Healthy aging was defined as survival to ≥85 years of age without a history of major age-related diseases and with no impairment of physical function or assistance in ADL. Physical function and ADL were assessed during study follow-up using the RAND 36-item Health Survey.[30] Impairment of physical function was based on a previous definition[31], which included the presence of any of the following limitations: limited at least "a little" on moderate activities (moving a table, vacuuming, bowling, or golfing; climbing one flight of stairs; walking more than one mile; walking several blocks; or bathing or dressing) or limited "a lot" on difficult performance items (running, lifting heavy objects, or strenuous sports; lifting or carrying groceries; climbing several flights of stairs; or bending, kneeling, or stooping). Being able to perform all six ADL (feeding, dressing and undressing, getting in and out of bed, taking a bath or shower, doing own

grocery shopping, and keeping track of and taking medicines) without any help was also a criterion for healthy aging. This resulted in three categories: healthy survivors, usual survivors, and non-survivors.

Statistical Analysis

Comparisons of survivors and non-survivors on baseline characteristics were performed using $\chi^2$ tests for categorical variables and two-sample t-tests or Wilcoxon's rank-sum tests for normally distributed and non-normally distributed continuous variables, respectively. Comparisons of healthy aging categories were performed using $\chi^2$ tests for categorical variables and analysis of variance or Kruskal-Wallis tests for continuous variables.

For all SNPs, count and reference alleles were defined. Separate analyses were conducted in white, Hispanic, and African-American women. Logistic regression models assuming a log-additive genetic effect were used to assess the association of each SNP with survival to age 85. For SNPs that were directly genotyped, SNP data were coded as 0/1/2 (indicating the number of count alleles present), and for imputed SNPs, the mean dosage of the count allele (a value between 0 and 2) was used. In the models, SNPs were used as continuous variables. All models adjusted for the top five principal components to control for population stratification. Models also adjusted for potential confounders including baseline age, WHI study component (CT or OS), education, marital status, BMI, physical activity, alcohol consumption, smoking behavior, and history of age-related diseases. Adjusting for genotyping source did not alter the findings (data not shown). Analyses were repeated with survival to age 90 as the outcome in white and African-American women only, as a limited number of Hispanic women survived to age

90. Multinomial logistic regression models were used to examine the association of each SNP with healthy aging in white women, using non-survivors as the reference category. Similar variable inclusion criteria as previously described were used. Healthy aging analyses were not performed in African-American or Hispanic women due to lower sample size in these groups. Because of varying patterns of missing data in covariates, multivariable logistic regression models had lower sample size resulting from the complete case analysis. Thus, models only adjusting for age and the first five principal components were also fit to make use of all of the available genetic data. Results are reported as odds ratios (ORs) and 95% confidence intervals (CIs). The ORs represent the change in odds of longevity for each additional copy of the count allele.

*P*-values were corrected for multiple testing using the Benjamini-Hochberg procedure[32], which controls for the false discovery rate and is a more powerful and less conservative approach than Bonferroni correction. *P*-values were two-tailed and considered nominally statistically significant at $P<0.05$ after correction. Analyses were conducted using Statistical Analysis Software, Version 9.3 (SAS Institute Inc., Cary, NC).

Power calculations for each racial/ethnic group were performed using Quanto[33] with the gene-only model, a disease trait phenotype, and unrelated individuals. Power estimates were made for a range of frequencies of the longevity allele and effect sizes, assuming an additive genetic model, a 2% likelihood of reaching age 85 or above[34], a type I error rate of 5%, and a two-sided hypothesis test. Power estimates were also calculated for analyses with survival to age 90 (assuming a 1% likelihood of reaching this

age) and healthy aging (assuming a 1% likelihood of achieving this phenotype) as the outcomes.

## Results

### Characteristics of Survivors and Non-Survivors

Comparisons of survivors and non-survivors on baseline characteristics among white, African-American, and Hispanic women are described in Tables 3.1-3.3. Of the women meeting the inclusion criteria for this study, 6,477 (74.8%) whites, 1,211 (65.2%) African-Americans, and 390 (72.4%) Hispanics survived to age 85, and 2,059 (53.2%), 343 (47.2%), and 83 (46.1%) survived to age 90, respectively. Average age at death among non-survivors was 79 (standard deviation [SD], 3.7; range, 67-84) years in whites, 78 (SD, 4.0; range, 67-84) years in African-Americans, and 79 (SD, 3.7; range, 67-84) years in Hispanics.

White, African-American, and Hispanic women were on average aged 71.9, 71.4, and 71.1 years at baseline, respectively. Among white women, those who lived to age 85 were more likely to be older at baseline, college graduates, current drinkers, married or living as married, and to have higher levels of physical activity (Table 3.1). They were less likely to have ever smoked, be obese, or have a history of age-related diseases. Similar findings were observed in African-American women (Table 3.2). In Hispanic women, those who survived to age 85 were more likely to be older at baseline, current drinkers, and have higher levels of physical activity; they were less likely to have ever smoked or have a history of age-related diseases. Education, marital status, and BMI did not vary by survival status in Hispanic women (Table 3.3).

Among 5,092 white women with longitudinal data on age-related diseases and physical impairment, 1,202 (23.6%) met the criteria for healthy aging (Table 3.4). White women with healthy aging were more likely to be college graduates, be current drinkers, have higher levels of physical activity, and to have never smoked. They were less likely to be obese at baseline. Among 1,141 African-American women, 214 (18.8%) were healthy survivors (Table 3.5). Differences between healthy survivors and other aging categories among African-American women were similar to those observed in white women. Among 324 Hispanic women, 91 (28.1%) were classified as healthy survivors (Table 3.6). Healthy survivors had higher levels of physical activity and were less likely to be obese. Healthy survival did not vary according to age, education, marital status, or smoking in Hispanic women.

SNPs Associated with Survival to Ages 85 and 90

In white women, no index SNP was significantly associated with survival to age 85 after correction for multiple testing (Table 3.7). However, in an analysis comparing women who lived to age 90 with those who died before this age, three of fourteen SNPs were replicated after correction for multiple testing (Table 3.8). The index SNP rs2075650, located in the *TOMM40* (translocase of outer mitochondrial membrane 40 homolog protein) gene on chromosome 19 near the *APOE* gene, was significantly associated with survival to age 90 in white women (corrected *P*-value <0.001). Each additional copy of the A allele increased the odds of living to 90 years by 34% (OR, 1.34; 95% CI, 1.15-1.58), after adjusting for age, BMI, physical activity, education, marital status, alcohol consumption, smoking, history of age-related diseases, and population stratification. Replication of rs4420638, located on chromosome 19 near the

apolipoprotein C1 (*APOC1*) gene and within 14kb of the *APOE* gene, was also observed (corrected *P*-value <0.001); carriers of the A allele had higher odds of survival to age 90 (OR, 1.39; 95% CI, 1.18-1.64). Of the two SNPs that define the three *APOE* isoforms, only rs429358 was significantly associated with survival to age 90 (OR, 1.47; 95% CI, 1.25-1.74 for carriage of the T vs. C allele; corrected *P*-value<0.001). To determine whether associations of rs2075650 and rs4420638 with survival to age 90 were independent of *APOE*, models additionally adjusting for rs7412 and rs429358 were fit. After adjustment for these SNPs, rs2075650 and rs4420638 were no longer significant (data not shown). Other SNPs, including rs2149954 located between the clathrin interactor 1 (*CLINT1*) and transcription factor COE1 (*EBF1*) genes, and SNPs located at the *FOXO3A* gene, failed to replicate in white women. Findings were similar in models only adjusting for age and population stratification, and rs7412 was also significantly associated with survival to age 90 in this analysis (Tables 3.9 and 3.10).

In African-American women, no index SNP or SNP in LD with any index SNP was significantly associated with survival to ages 85 or 90 (Tables 3.11 and 3.12). Findings were similar in models only adjusting for age and population stratification (Tables 3.13 and 3.14). In Hispanic women, no SNP was significantly associated with survival to age 85 after correction for multiple testing (Table 3.15); analyses for survival to age 90 were not performed due to inadequate sample size. However, in models only adjusting for age and population stratification among Hispanic women, seven SNPs in LD with the index SNP rs2149954 (located between the *CLINT1* and *EBF1* genes) were significantly associated with survival to age 85 after correction for multiple testing (*P*-value = 0.037; Table 3.16). To determine potential mechanisms that may explain the link

between these SNPs and longevity, associations with age-related diseases (CHD, stroke, diabetes, or cancer), hypertension, and diastolic and systolic blood pressures were evaluated. However, none of the SNPs was associated with any of these phenotypes.

SNPs Associated with Healthy Aging

Analyses for healthy aging were only performed in white women due to small sample sizes of survival categories in the other ethnic groups. Of the fourteen index SNPs tested, rs4420638 near the *APOC1* gene and rs429358 at *APOE* were significantly associated with healthy aging (Table 3.17; *P*-value = 0.021 and *P*-value = 0.021, respectively). The odds of healthy survival were significantly higher in carriers of the A allele at rs4420638 (OR, 1.28; 95% CI, 1.08-1.52) and in carriers of the T allele at rs429358 (OR, 1.32; 95% CI, 1.11-1.57). After adjustment for the *APOE* SNPs rs7412 and rs429358, rs4420638 was no longer significantly associated with healthy survival (data not shown). In analyses adjusting only for age and population stratification, findings were similar (Table 3.18).

**Discussion**

This was the first study to determine whether genetic factors previously associated with longevity in populations of European descent replicate in African-American and Hispanic women. No index SNP or SNP in LD with any index SNP was associated with prolonged survival in African-American women. In Hispanic women, SNPs in LD with a novel locus (rs2149954) identified as being associated with longevity in a recent GWAS among European-Americans[16] were associated with survival to age 85. Among white women, no SNP was associated with survival to age 85, but three were

associated with survival to age 90: rs2075650, located in the *TOMM40* gene near *APOE*; rs4420638, located near the *APOC1* and *APOE* genes; and rs429358, one of two SNPs defining the three *APOE* isoforms. Finally, rs4420638 near the *APOC1* gene and rs429358 at *APOE* were significantly associated with healthy aging in white women. Our observations extend previous findings that *APOE* is associated with longevity in white women but do not implicate variants at this gene as longevity-promoting in African-American or Hispanic women.

In previous GWAS, only genetic variants near *APOE* have reached genome-wide significance.[13-17] In a meta-analysis of GWAS among Europeans including 4,149 nonagenarian cases and 7,582 younger controls, rs2075650 on chromosome 19 was the only SNP significantly associated ($P = 3.39 \times 10^{-17}$) with survival to old age[13]; the association was present in both men and women. However, the association of rs2075650 with survival to age 90 was no longer significant after adjusting for rs7412 and rs429358, the two *APOE* genetic variants. Similarly, among white women, we observed that rs2075650 was no longer significantly associated with survival to age 90 after adjusting for these SNPs, indicating that *TOMM40* does not have an independent effect on survival but rather tags variation at *APOE*. Of the two *APOE* SNPs, only rs429358, which tags the effects of the deleterious *APOE* ε4 allele, was significantly associated with longevity, with a 47% increased odds of survival to 90 years for carriers of the T allele. We also observed a significant association of rs4420638, located near the *APOC1* gene, with survival to age 90; however, this association was not independent of *APOE*, consistent with a previous study.[17] None of these SNPs was associated with survival to age 85 in

white women, supporting the observation that genetic factors may be of greater importance at more advanced ages such as 90 years and above.[3]

In the current study, rs4420638 and rs429358 were significantly associated with healthy aging in white women. Although healthy aging has been largely studied in relation to behavioral factors, limited studies have evaluated the association of genetic factors with healthy aging.[2,3,5,6] A study in 1,344 Italians observed a higher prevalence of the *APOE* ε2 allele in centenarian men (who were free of cognitive impairment, functional limitations, and diseases including cerebrovascular disease, nephropathy, and end-stage renal disease) than in controls younger than 60 years.[6] Indeed, it is possible that healthy aging may have a genetic basis. A recent investigation among the Health and Retirement Study cohort showed that approximately one-fifth of centenarians did not have any chronic diseases in their 80s or 90s and delayed disease until they reached later ages, and 21% were never diagnosed with a chronic disease.[35] Additionally, one-fifth of centenarians never had disability, and one-fourth survived with disability. Mechanisms allowing exceptional survivors to markedly delay or avoid disease and disability entirely are currently unknown, but it is possible that genetic factors may play a role. A previous study showed that nonagenarians carry the same number of risk alleles for chronic diseases including cardiovascular disease, type 2 diabetes, and cancer as younger controls, suggesting that there may be genetic variants specifically promoting longevity, healthy aging, and a delay in disease.[36]

The association of variation at *APOE* with longevity and healthy aging may be explained by several mechanisms. APOE is a lipoprotein that is a major carrier of cholesterol and lipids across various tissues. The APOE4 isoform is associated with

hyperlipidemia and hypercholesterolemia, and has been linked to cardiovascular diseases including coronary heart disease and stroke.[37,38] Additionally, APOE is involved in lipid transport to the brain, and carriage of the ε4 allele has been associated with increased risk of Alzheimer's disease.[20]

In the current study, no variant at the *FOXO3A* gene, which is involved in the insulin/insulin-like growth factor 1 signaling pathway, was replicated in any ethnic group. Although variation at *FOXO3A* has been associated with longevity in prior candidate gene association studies among German, Italian, Japanese, American, and Asian populations[8-12,39], most GWAS have failed to find significant associations with this gene at the genome-wide level.[14-17] However, a recent GWAS identified rs10457810 as being strongly associated with surviving to age 90 in a conditional analysis, which analyzes aggregate-level data.[13] The association of *FOXO3A* with longevity has been shown to be stronger in persons aged ≥95 and especially in centenarians[3,8,11], which may partially explain the lack of an association between SNPs at *FOXO3A* and longevity in our study. This is consistent with the observation that the role of genetic variants in attaining longevity may become more important at extreme ages.[2,3] Given these inconsistent findings, additional studies in larger cohorts of exceptionally aged individuals will be needed to evaluate the relationship between *FOXO3A* and longevity.

SNPs previously associated with longevity in populations of European descent failed to replicate in African-American women, and the majority did not replicate in Hispanic women. Lack of replication may be partially due to smaller sample size and insufficient power compared with whites in these groups; this is a likely explanation, as effect sizes for SNPs were similar to those among white women. There is currently a

paucity of literature on factors associated with longevity in ethnic minorities. Although no study has evaluated genetic factors in relation to longevity in African-Americans or Hispanics, GWAS examining different phenotypes in these ethnic groups are emerging. For example, GWAS and replication studies of phenotypes such as type 2 diabetes, cancer, and obesity have revealed that there are ethnic variations in SNP associations with various health outcomes.[40-42] They have also revealed novel loci associated with these phenotypes, suggesting that different genes and mechanisms may influence longevity in diverse populations.

Although no SNP was associated with longevity in Hispanics in the multivariable models, in analyses only adjusting for age and population stratification several SNPs in LD with rs2149954, located between *CLINT1* and *EBF1*, were significant after correction for multiple testing. The lack of associations after *P*-value correction in the fully adjusted models may be due to lower statistical power resulting from smaller sample size, as these models were fit using only cases with complete information. The models adjusting only for age and population stratification had no missing data and thus had a higher sample size and power. A study in >12,000 nonagenarians and younger controls recently identified rs2149954 as being significantly associated with longevity at the genome-wide level.[16] This study also observed that rs2149954 was associated with cardiovascular disease and diastolic and systolic blood pressures. However, in our study, SNPs in LD with rs2149954 were not associated with any of these phenotypes, suggesting that there may be other mechanisms explaining the association of these genetic variants with longevity in Hispanics.

This study had several limitations. The number of African-American and Hispanic women surviving to age 85 was much lower than the number of whites surviving to this age, and consequently there was lower power to detect effect sizes previously reported in European-Americans in these ethnic groups (see Tables 3.19-3.24). The older WHI participants in this study may have been healthier at baseline than the general population in the same age group. Furthermore, women who enrolled for additional follow-up were more likely to be white, educated, and healthier at baseline than those who withdrew, thus our findings may be biased by selective attrition. It is possible that those who dropped out were more likely to be cognitively impaired, thus biasing *APOE* findings. Finally, our study consisted only of women, and therefore we could not examine sex differences in the associations of SNPs with longevity and healthy aging.

Strengths of this study included a large, multi-ethnic sample of women. This study was novel in that it was the first to evaluate the association of genetic factors with exceptional survival in African-American and Hispanic women. We made use of imputed genetic data to maximize the availability of genetic information for the longevity analyses. Additional strengths include the prospective design with up to 21 years of follow-up, high retention of study participants over time, and adjudicated outcome ascertainment. Finally, unlike prior studies on genetic factors and longevity, this study included a cohort of women with a narrow age range, thus limiting any potential bias due to birth cohort effects.

In conclusion, we observed that *APOE* was associated with advanced survival in white women and also observed that this gene was associated with aging free of chronic

diseases and physical impairment with the ability to perform all ADL in this group. SNPs previously associated with longevity in European populations failed to replicate in African-American women. In Hispanic women, SNPs in LD with a novel SNP recently identified as being associated with longevity in Europeans were significantly associated with survival to age 85. Candidate gene association studies and GWAS of longevity, which have not been conducted in African-Americans and Hispanics, will be important in identifying novel loci and biologic pathways regulating lifespan in these ethnic groups. Additional genetic studies of healthy aging are also needed to confirm whether *APOE* and other genes are associated with disease- and disability-free survival.

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Chapter 3, in full, has been submitted for publication of the material as it may appear in *Human Molecular Genetics*. Shadyab, Aladdin H.; Jain, Sonia; Kooperberg, Charles; Reiner, Alexander P.; Manson, JoAnn E.; Hohensee, Chancellor; Macera, Caroline A.; Shaffer, Richard A.; Gallo, Linda C.; LaCroix, Andrea Z. The dissertation author was the primary investigator and author of this paper.

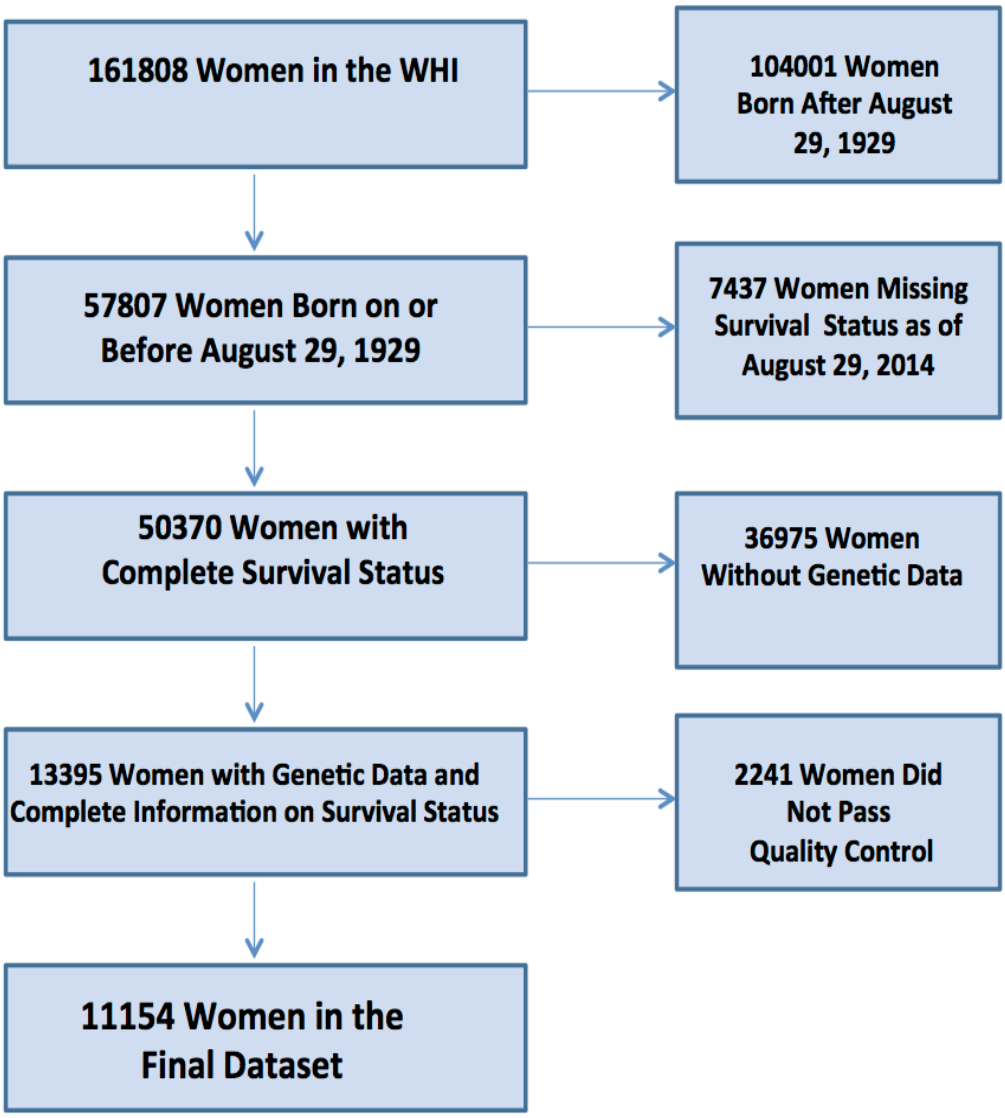


Figure 3.1: Derivation of Final Analytic Sample

Table 3.1: Comparisons of Survivors to Age 85 and Non-Survivors on Baseline Characteristics among White Women

| Characteristic | Total (n=8656) No. (%) | Survived to age 85 (n=6477) No. (%) | Died before age 85 (n=2179) No. (%) | *P*-value |
|---|---|---|---|---|
| WHI component (n=8656) | | | | |
| Clinical Trial | 6669 (77.0) | 5071 (78.3) | 1598 (73.3) | <0.001 |
| Observational Study | 1987 (23.0) | 1406 (21.7) | 581 (26.7) | |
| Baseline age, years | | | | |
| Mean (SD) | 71.9 (3.4) | 72.3 (3.4) | 70.7 (3.2) | <0.001 |
| Median (range) | 72.0 (64-81) | 72.0 (64-81) | 70.0 (64-79) | |
| Educational level (n=8622) | | | | |
| Less than high school | 438 (5.1) | 291 (4.5) | 147 (6.8) | |
| High school | 1728 (20.0) | 1291 (20.0) | 437 (20.1) | <0.001 |
| Some college | 3523 (40.9) | 2639 (40.9) | 884 (40.7) | |
| College graduate | 2933 (34.0) | 2231 (34.6) | 702 (32.4) | |
| Marital status (n=8629) | | | | |
| Married or living as married | 4540 (52.6) | 3444 (53.4) | 1096 (50.4) | |
| Widowed | 2880 (33.4) | 2167 (33.6) | 713 (32.8) | <0.001 |
| Divorced or separated | 882 (10.2) | 602 (9.3) | 280 (12.9) | |
| Never married | 327 (3.8) | 242 (3.8) | 85 (3.9) | |
| Smoking behavior (n=8537) | | | | |
| Never smoked | 4599 (53.9) | 3658 (57.2) | 941 (43.9) | |
| Past smoker | 3462 (40.6) | 2506 (39.2) | 956 (44.6) | <0.001 |
| Current smoker | 476 (5.6) | 228 (3.6) | 248 (11.6) | |
| Alcohol intake (n=8603) | | | | |
| Nondrinker | 923 (10.7) | 683 (10.6) | 240 (11.1) | |
| Past drinker | 1613 (18.8) | 1126 (17.5) | 487 (22.5) | <0.001 |
| Current drinker | 6067 (70.5) | 4628 (71.9) | 1439 (66.4) | |
| Recreational physical activity, MET-hours/week | | | | |
| Mean (SD) | 11.7 (12.7) | 12.2 (12.8) | 10.4 (12.4) | <0.001 |
| Median (range) | 8.0 (0-134.2) | 8.4 (0-134.2) | 6.9 (0-119.0) | |
| Body mass index (n=8603) | | | | |
| Underweight (<18.5) | 86 (1.0) | 52 (0.8) | 34 (1.6) | |
| Normal weight (18.5-24.9) | 2917 (33.9) | 2212 (34.3) | 705 (32.6) | <0.001 |
| Overweight (25.0-29.9) | 3126 (36.3) | 2389 (37.1) | 737 (34.1) | |
| Obese (≥30) | 2474 (28.8) | 1788 (27.8) | 686 (31.7) | |
| History of major age-related diseases (n=8656) | | | | |
| Coronary heart disease | 1044 (12.1) | 503 (7.8) | 541 (24.8) | <0.001 |
| Stroke | 771 (8.9) | 398 (6.1) | 373 (17.1) | <0.001 |
| Cancer (excluding non-melanoma skin cancer) | 2408 (27.8) | 1317 (20.3) | 1091 (50.1) | <0.001 |
| Diabetes | 1288 (14.9) | 870 (13.4) | 418 (19.2) | <0.001 |
| Hip fracture | 1362 (15.7) | 914 (14.1) | 448 (20.6) | <0.001 |
| ≥1 major age-related disease | 4964 (57.4) | 3101 (47.9) | 1863 (85.5) | <0.001 |

Table 3.2: Comparisons of Survivors to Age 85 and Non-Survivors on Baseline Characteristics among African-American Women

| Characteristic | Total (n=1858) No. (%) | Survived to age 85 (n=1211) No. (%) | Died before age 85 (n=647) No. (%) | *P*-value |
|---|---|---|---|---|
| WHI component (n=1858) | | | | |
| Clinical Trial | 908 (48.9) | 622 (51.4) | 286 (44.2) | <0.01 |
| Observational Study | 950 (51.1) | 589 (48.6) | 361 (55.8) | |
| Baseline age, years | | | | |
| Mean (SD) | 71.4 (3.4) | 71.9 (3.4) | 70.6 (3.4) | <0.001 |
| Median (range) | 71.0 (64-79) | 71.0 (64-79) | 70.0 (64-79) | |
| Educational level (n=1839) | | | | |
| Less than high school | 322 (17.5) | 173 (14.4) | 149 (23.2) | |
| High school | 254 (13.8) | 160 (13.4) | 94 (14.7) | <0.001 |
| Some college | 617 (33.6) | 397 (33.1) | 220 (34.3) | |
| College graduate | 646 (35.1) | 468 (39.1) | 178 (27.8) | |
| Marital status (n=1845) | | | | |
| Married or living as married | 592 (32.1) | 423 (35.2) | 169 (26.3) | |
| Widowed | 776 (42.1) | 496 (41.3) | 280 (43.6) | <0.001 |
| Divorced or separated | 404 (21.9) | 242 (20.1) | 162 (25.2) | |
| Never married | 73 (4.0) | 41 (3.4) | 32 (5.0) | |
| Smoking behavior (n=1798) | | | | |
| Never smoked | 916 (51.0) | 640 (54.5) | 276 (44.2) | |
| Past smoker | 723 (40.2) | 466 (40.0) | 257 (41.2) | <0.001 |
| Current smoker | 159 (8.8) | 68 (5.8) | 91 (14.6) | |
| Alcohol intake (n=1823) | | | | |
| Nondrinker | 344 (18.9) | 230 (19.4) | 114 (18.0) | |
| Past drinker | 647 (35.5) | 371 (31.2) | 276 (43.5) | <0.001 |
| Current drinker | 832 (45.6) | 587 (49.4) | 245 (38.6) | |
| Recreational physical activity, MET-hours/week | | | | |
| Mean (SD) | 9.7 (12.6) | 10.5 (13.1) | 8.2 (11.6) | <0.001 |
| Median (range) | 5.3 (0-96.6) | 6.3 (0-94.8) | 4.5 (0-96.6) | |
| Body mass index (n=1843) | | | | |
| Underweight (<18.5) | 14 (0.8) | 7 (0.6) | 7 (1.1) | |
| Normal weight (18.5-24.9) | 344 (18.7) | 243 (20.2) | 101 (15.8) | <0.001 |
| Overweight (25.0-29.9) | 656 (35.6) | 451 (37.5) | 205 (32.0) | |
| Obese (≥30) | 829 (45.0) | 501 (41.7) | 328 (51.2) | |
| History of major age-related diseases (n=1858) | | | | |
| Coronary heart disease | 298 (16.0) | 100 (8.3) | 198 (30.6) | <0.001 |
| Stroke | 218 (11.7) | 104 (8.6) | 114 (17.6) | <0.001 |
| Cancer (excluding non-melanoma skin cancer) | 480 (25.8) | 200 (16.5) | 280 (43.3) | <0.001 |
| Diabetes | 546 (29.4) | 313 (25.9) | 233 (36.0) | <0.001 |
| Hip fracture | 51 (2.7) | 35 (2.9) | 16 (2.5) | 0.60 |
| ≥1 major age-related disease | 1122 (60.4) | 579 (47.8) | 543 (83.9) | <0.001 |

Table 3.3: Comparisons of Survivors to Age 85 and Non-Survivors on Baseline Characteristics among Hispanic Women

| Characteristic | Total (n=539) No. (%) | Survived to age 85 (n=390) No. (%) | Died before age 85 (n=149) No. (%) | *P*-value |
|---|---|---|---|---|
| WHI component (n=539) | | | | |
| Clinical Trial | 231 (42.9) | 174 (44.6) | 57 (38.3) | 0.18 |
| Observational Study | 308 (57.1) | 216 (55.4) | 92 (61.7) | |
| Baseline age, years | | | | |
| Mean (SD) | 71.1 (3.1) | 71.5 (3.1) | 70.3 (3.1) | <0.001 |
| Median (range) | 71.0 (65-79) | 71.0 (65-79) | 70.0 (65-79) | |
| Educational level (n=530) | | | | |
| Less than high school | 125 (23.6) | 83 (21.6) | 42 (28.8) | |
| High school | 98 (18.5) | 76 (19.8) | 22 (15.1) | 0.30 |
| Some college | 193 (36.4) | 141 (36.7) | 52 (35.6) | |
| College graduate | 114 (21.5) | 84 (21.9) | 30 (20.6) | |
| Marital status (n=530) | | | | |
| Married or living as married | 282 (53.2) | 208 (54.2) | 74 (50.7) | |
| Widowed | 157 (29.6) | 117 (30.5) | 40 (27.4) | 0.16 |
| Divorced or separated | 73 (13.8) | 45 (11.7) | 28 (19.2) | |
| Never married | 18 (3.4) | 14 (3.7) | 4 (2.7) | |
| Smoking behavior (n=526) | | | | |
| Never smoked | 361 (68.6) | 273 (71.5) | 88 (61.1) | |
| Past smoker | 147 (28.0) | 100 (26.2) | 47 (32.6) | 0.02 |
| Current smoker | 18 (3.4) | 9 (2.4) | 9 (6.3) | |
| Alcohol intake (n=524) | | | | |
| Nondrinker | 106 (20.2) | 75 (19.7) | 31 (21.5) | |
| Past drinker | 135 (25.8) | 85 (22.4) | 50 (34.7) | 0.01 |
| Current drinker | 283 (54.0) | 220 (57.9) | 63 (43.8) | |
| Recreational physical activity, MET-hours/week | | | | |
| Mean (SD) | 11.3 (12.8) | 12.1 (13.3) | 9.4 (11.4) | 0.02 |
| Median (range) | 7.5 (0-75.8) | 7.5 (0-75.8) | 5.3 (0-55.5) | |
| Body mass index (n=533) | | | | |
| Underweight (<18.5) | 2 (0.4) | 2 (0.5) | 0 | |
| Normal weight (18.5-24.9) | 156 (29.3) | 121 (31.4) | 35 (23.8) | |
| Overweight (25.0-29.9) | 215 (40.3) | 158 (40.9) | 57 (38.8) | 0.08 |
| Obese (≥30) | 160 (30.0) | 105 (27.2) | 55 (37.4) | |
| History of major age-related diseases (n=539) | | | | |
| Coronary heart disease | 41 (7.6) | 15 (3.9) | 26 (17.5) | <0.001 |
| Stroke | 47 (8.7) | 18 (4.6) | 29 (19.5) | <0.001 |
| Cancer (excluding non-melanoma skin cancer) | 131 (24.3) | 64 (16.4) | 67 (45.0) | <0.001 |
| Diabetes | 112 (20.8) | 71 (18.2) | 41 (27.5) | 0.02 |
| Hip fracture | 20 (3.7) | 15 (3.9) | 5 (3.4) | 0.79 |
| ≥1 major age-related disease | 261 (48.4) | 147 (38.0) | 114 (76.5) | <0.001 |

Table 3.4: Comparisons of Baseline Characteristics by Survival Phenotype among White Women

| Characteristic | Total (n=5092) No. (%) | Healthy survivor to age 85[a] (n=1202) No. (%) | Usual survivor to age 85 (n=1711) No. (%) | Died before age 85 (n=2179) No. (%) | *P*-value |
|---|---|---|---|---|---|
| WHI component (n=5092) | | | | | |
| Clinical Trial | 3968 (77.9) | 1067 (88.8) | 1303 (76.2) | 1598 (73.3) | <0.001 |
| Observational Study | 1124 (22.1) | 135 (11.2) | 408 (23.9) | 581 (26.7) | |
| Baseline age, years | | | | | |
| Mean (SD) | 71.1 (2.9) | 71.4 (2.7) | 71.3 (2.7) | 70.7 (3.2) | <0.001 |
| Median (range) | 71.0 (64-79) | 71.0 (65-77) | 71.0 (65-77) | 70.0 (64-79) | |
| Educational level (n=5072) | | | | | |
| Less than high school | 260 (5.1) | 34 (2.8) | 79 (4.6) | 147 (6.8) | |
| High school | 1043 (20.6) | 260 (21.7) | 346 (20.3) | 437 (20.1) | <0.001 |
| Some college | 2027 (40.0) | 452 (37.7) | 691 (40.6) | 884 (40.7) | |
| College graduate | 1742 (34.4) | 453 (37.8) | 587 (34.5) | 702 (32.4) | |
| Marital status (n=5077) | | | | | |
| Married or living as married | 2745 (54.1) | 677 (56.5) | 972 (57.0) | 1096 (50.4) | |
| Widowed | 1602 (31.6) | 366 (30.6) | 523 (30.7) | 713 (32.8) | <0.001 |
| Divorced or separated | 543 (10.7) | 116 (9.7) | 147 (8.6) | 280 (12.9) | |
| Never married | 187 (3.7) | 39 (3.3) | 63 (3.7) | 85 (3.9) | |
| Smoking behavior (n=5023) | | | | | |
| Never smoked | 2593 (51.6) | 700 (58.5) | 952 (56.6) | 941 (43.9) | |
| Past smoker | 2099 (41.8) | 462 (38.6) | 681 (40.5) | 956 (44.6) | <0.001 |
| Current smoker | 331 (6.6) | 35 (2.9) | 48 (2.9) | 248 (11.6) | |
| Alcohol intake (n=5067) | | | | | |
| Nondrinker | 509 (10.1) | 106 (8.9) | 163 (9.6) | 240 (11.1) | |
| Past drinker | 959 (18.9) | 160 (13.4) | 312 (18.3) | 487 (22.5) | <0.001 |
| Current drinker | 3599 (71.0) | 932 (77.8) | 1228 (72.1) | 1439 (66.4) | |
| Recreational physical activity, MET-hours/week | | | | | |
| Mean (SD) | 11.7 (13.0) | 13.5 (13.4) | 12.0 (13.2) | 10.4 (12.4) | <0.001 |
| Median (range) | 7.5 (0-134.2) | 10.5 (0-134.2) | 7.5 (0-100) | 6.9 (0-119.0) | |
| Body mass index (n=5060) | | | | | |
| Underweight (<18.5) | 49 (1.0) | 5 (0.4) | 10 (0.6) | 34 (1.6) | |
| Normal weight (18.5-24.9) | 1716 (33.9) | 470 (39.3) | 541 (31.8) | 705 (32.6) | <0.001 |
| Overweight (25.0-29.9) | 1790 (35.4) | 451 (37.7) | 602 (35.4) | 737 (34.1) | |
| Obese (≥30) | 1505 (29.7) | 270 (22.6) | 549 (32.3) | 686 (31.7) | |

[a]Healthy survival defined as survival to ≥85 years of age without a history of major age-related diseases (coronary heart disease, stroke, cancer [excluding non-melanoma skin cancer], diabetes, and hip fracture) with no impairment of physical function or assistance in activities of daily living

Table 3.5: Comparisons of Baseline Characteristics by Survival Phenotype among African-American Women

| Characteristic | Total (n=1141) No. (%) | Healthy survivor to age 85[a] (n=214) No. (%) | Usual survivor to age 85 (n=280) No. (%) | Died before age 85 (n=647) No. (%) | *P*-value |
|---|---|---|---|---|---|
| WHI component (n=1141) | | | | | |
| Clinical Trial | 556 (48.7) | 123 (57.5) | 147 (52.5) | 286 (44.2) | <0.01 |
| Observational Study | 585 (51.3) | 91 (42.5) | 133 (47.5) | 361 (55.8) | |
| Baseline age, years | | | | | |
| Mean (SD) | 70.9 (3.1) | 71.2 (2.7) | 71.4 (2.7) | 70.6 (3.4) | <0.001 |
| Median (range) | 71.0 (64-79) | 71.0 (65-77) | 71.0 (65-77) | 70.0 (64-79) | |
| Educational level (n=1128) | | | | | |
| Less than high school | 204 (18.1) | 17 (8.1) | 38 (13.7) | 149 (23.2) | |
| High school | 154 (13.7) | 27 (12.9) | 33 (11.9) | 94 (14.7) | <0.001 |
| Some college | 384 (34.0) | 69 (32.9) | 95 (34.3) | 220 (34.3) | |
| College graduate | 386 (34.2) | 97 (46.2) | 111 (40.1) | 178 (27.8) | |
| Marital status (n=1132) | | | | | |
| Married or living as married | 347 (30.7) | 81 (38.2) | 97 (35.0) | 169 (26.3) | |
| Widowed | 480 (42.4) | 85 (40.1) | 115 (41.5) | 280 (43.6) | 0.01 |
| Divorced or separated | 256 (22.6) | 42 (19.8) | 52 (18.8) | 162 (25.2) | |
| Never married | 49 (4.3) | 4 (1.9) | 13 (4.7) | 32 (5.0) | |
| Smoking behavior (n=1105) | | | | | |
| Never smoked | 530 (48.0) | 113 (54.3) | 141 (51.7) | 276 (44.2) | |
| Past smoker | 450 (40.7) | 79 (38.0) | 114 (41.8) | 257 (41.2) | <0.01 |
| Current smoker | 125 (11.3) | 16 (7.7) | 18 (6.6) | 91 (14.6) | |
| Alcohol intake (n=1121) | | | | | |
| Nondrinker | 208 (18.6) | 36 (17.0) | 58 (21.2) | 114 (18.0) | |
| Past drinker | 426 (38.0) | 63 (29.7) | 87 (31.8) | 276 (43.5) | <0.001 |
| Current drinker | 487 (43.4) | 113 (53.3) | 129 (47.1) | 245 (38.6) | |
| Recreational physical activity, MET-hours/week | | | | | |
| Mean (SD) | 9.3 (12.0) | 12.4 (13.3) | 9.3 (11.6) | 8.2 (11.6) | <0.001 |
| Median (range) | 5.3 (0-96.6) | 8.3 (0-73.5) | 5.0 (0-87.1) | 4.5 (0-96.6) | |
| Body mass index (n=1133) | | | | | |
| Underweight (<18.5) | 8 (0.7) | 0 | 1 (0.4) | 7 (1.1) | |
| Normal weight (18.5-24.9) | 203 (17.9) | 61 (28.5) | 41 (14.8) | 101 (15.8) | <0.001 |
| Overweight (25.0-29.9) | 391 (34.5) | 86 (40.2) | 100 (36.0) | 205 (32.0) | |
| Obese (≥30) | 531 (46.9) | 67 (31.3) | 136 (48.9) | 328 (51.2) | |

[a]Healthy survival defined as survival to ≥85 years of age without a history of major age-related diseases (coronary heart disease, stroke, cancer [excluding non-melanoma skin cancer], diabetes, and hip fracture) with no impairment of physical function or assistance in activities of daily living

Table 3.6: Comparisons of Baseline Characteristics by Survival Phenotype among Hispanic Women

| Characteristic | Total (n=324) No. (%) | Healthy survivor to age 85 (n=91) No. (%) | Usual survivor to age 85 (n=84) No. (%) | Died before age 85 (n=149) No. (%) | *P*-value |
|---|---|---|---|---|---|
| WHI component (n=324) | | | | | |
| Clinical Trial | 135 (41.7) | 42 (46.2) | 36 (42.9) | 57 (38.3) | 0.47 |
| Observational Study | 189 (58.3) | 49 (53.9) | 48 (57.1) | 92 (61.7) | |
| Baseline age, years | | | | | |
| Mean (SD) | 70.6 (2.9) | 71.0 (2.5) | 70.6 (2.8) | 70.3 (3.1) | 0.15 |
| Median (range) | 70.0 (65-79) | 70.0 (66-76) | 70.0 (65-76) | 70.0 (65-79) | |
| Educational level (n=318) | | | | | |
| Less than high school | 66 (20.8) | 11 (12.5) | 13 (15.5) | 42 (28.8) | |
| High school | 58 (18.2) | 17 (19.3) | 19 (22.6) | 22 (15.1) | 0.06 |
| Some college | 123 (38.7) | 36 (40.9) | 35 (41.7) | 52 (35.6) | |
| College graduate | 71 (22.3) | 24 (27.3) | 17 (20.2) | 30 (20.6) | |
| Marital status (n=319) | | | | | |
| Married or living as married | 170 (53.3) | 49 (54.4) | 47 (56.6) | 74 (50.7) | |
| Widowed | 91 (28.5) | 25 (27.8) | 26 (31.3) | 40 (27.4) | 0.55 |
| Divorced or separated | 48 (15.1) | 13 (14.4) | 7 (8.4) | 28 (19.2) | |
| Never married | 10 (3.1) | 3 (3.3) | 3 (3.6) | 4 (2.7) | |
| Smoking behavior (n=315) | | | | | |
| Never smoked | 212 (67.3) | 64 (71.9) | 60 (73.2) | 88 (61.1) | |
| Past smoker | 90 (28.6) | 23 (25.8) | 20 (24.4) | 47 (32.6) | 0.20 |
| Current smoker | 13 (4.1) | 2 (2.3) | 2 (2.4) | 9 (6.3) | |
| Alcohol intake (n=315) | | | | | |
| Nondrinker | 62 (19.7) | 16 (18.2) | 15 (18.1) | 31 (21.5) | |
| Past drinker | 88 (27.9) | 23 (26.1) | 15 (18.1) | 50 (34.7) | 0.04 |
| Current drinker | 165 (52.4) | 49 (55.7) | 53 (63.9) | 63 (43.8) | |
| Recreational physical activity, MET-hours/week | | | | | |
| Mean (SD) | 11.5 (12.7) | 15.8 (15.1) | 10.4 (11.1) | 9.4 (11.4) | <0.001 |
| Median (range) | 7.5 (0-75.8) | 12.3 (0-75.8) | 7.5 (0-49) | 5.3 (0-55.5) | |
| Body mass index (n=321) | | | | | |
| Normal weight (18.5-24.9) | 95 (29.6) | 33 (36.3) | 27 (32.5) | 35 (23.8) | |
| Overweight (25.0-29.9) | 134 (41.7) | 43 (47.3) | 34 (41.0) | 57 (38.8) | 0.01 |
| Obese (≥30) | 92 (28.7) | 15 (16.5) | 22 (26.5) | 55 (37.4) | |

Table 3.7: Associations of Significant Loci from Previous Studies with Survival to Age 85 in White Women

| SNP | References | Chromosome | Position | Count allele/ Reference allele | OR (95% CI)[b] n=7903 | Uncorrected *P* value | Corrected *P* value |
|---|---|---|---|---|---|---|---|
| *TOMM40*[a] | | | | | | | |
| rs2075650 | 13-15 | 19 | 45395619 | A/G | 1.15 (1.02-1.30)[c] | 0.020 | 0.091 |
| *APOC1*[a] | | | | | | | |
| rs4420638 | 16,17 | 19 | 45422946 | A/G | 1.17 (1.03-1.32)[c] | 0.015 | 0.091 |
| *APOE*[a] | | | | | | | |
| rs7412 | 15 | 19 | 45412079 | C/T | 0.87 (0.74-1.02)[c] | 0.093 | 0.222 |
| rs429358 | 15 | 19 | 45411941 | T/C | 1.18 (1.04-1.34)[c] | 0.009 | 0.091 |
| *CLINT1, EBF1*[a] | | | | | | | |
| rs2149954 | 15 | 5 | 157820602 | C/T | 0.91 (0.84-0.99) | 0.026 | 0.091 |
| *FOXO3A*[a] | | | | | | | |
| rs10457180 | 13 | 6 | 108965039 | A/G | 0.96 (0.88-1.05) | 0.335 | 0.559 |
| rs2764264 | 8-10 | 6 | 108934461 | T/C | 0.97 (0.88-1.05) | 0.419 | 0.587 |
| rs13217795 | 8-10 | 6 | 108974098 | T/C | 0.96 (0.88-1.05) | 0.354 | 0.559 |
| rs2802292 | 8,9,13 | 6 | 108908518 | T/G | 0.93 (0.86-1.01) | 0.095 | 0.222 |
| rs9400239 | 11 | 6 | 108977663 | C/T | 0.96 (0.88-1.05) | 0.360 | 0.559 |

SNP, single nucleotide polymorphism
[a]Gene or nearest genes
[b]Multivariable model adjusts for study membership (CT or OS), age, BMI, physical activity, education, marital status, alcohol consumption, smoking behavior, history of age-related diseases, and first five principal components
[c]N=7659

Table 3.7: Associations of Significant Loci from Previous Studies with Survival to Age 85 in White Women, Continued

| SNP | References | Chromosome | Position | Count allele/ Reference allele | OR (95% CI)[b] n=7903 | Uncorrected *P* value | Corrected *P* value |
|---|---|---|---|---|---|---|---|
| rs3800231 | 11 | 6 | 108998266 | G/A | 0.98 (0.90-1.07) | 0.645 | 0.694 |
| rs479744 | 10,11 | 6 | 109020032 | G/T | 1.02 (0.92-1.12) | 0.750 | 0.750 |
| rs1935949 | 12 | 6 | 108999287 | G/A | 0.98 (0.90-1.07) | 0.634 | 0.694 |
| rs4946935 | 12 | 6 | 109000742 | G/A | 0.98 (0.90-1.07) | 0.618 | 0.694 |

SNP, single nucleotide polymorphism
[a]Gene or nearest genes
[b]Multivariable model adjusts for study membership (CT or OS), age, BMI, physical activity, education, marital status, alcohol consumption, smoking behavior, history of age-related diseases, and first five principal components
[c]N=7659

Table 3.8: Associations of Significant Loci from Previous Studies with Survival to Age 90 in White Women

| SNP | References | Chromosome | Position | Count allele/ Reference allele | OR (95% CI)[b] n=3503 | Uncorrected *P* value | Corrected *P* value |
|---|---|---|---|---|---|---|---|
| *TOMM40*[a] | | | | | | | |
| rs2075650 | 13-15 | 19 | 45395619 | A/G | 1.34 (1.15-1.58)[c] | <0.001 | <0.001 |
| *APOC1*[a] | | | | | | | |
| rs4420638 | 16,17 | 19 | 45422946 | A/G | 1.39 (1.18-1.64)[c] | <0.001 | <0.001 |
| *APOE*[a] | | | | | | | |
| rs7412 | 15 | 19 | 45412079 | C/T | 0.79 (0.65-0.96)[c] | 0.020 | 0.069 |
| rs429358 | 15 | 19 | 45411941 | T/C | 1.47 (1.25-1.74)[c] | <0.001 | <0.001 |
| *CLINT1, EBF1*[a] | | | | | | | |
| rs2149954 | 15 | 5 | 157820602 | C/T | 0.94 (0.85-1.05) | 0.270 | 0.371 |
| *FOXO3A*[a] | | | | | | | |
| rs10457180 | 13 | 6 | 108965039 | A/G | 1.06 (0.95-1.18) | 0.318 | 0.371 |
| rs2764264 | 8-10 | 6 | 108934461 | T/C | 1.06 (0.95-1.19) | 0.294 | 0.371 |
| rs13217795 | 8-10 | 6 | 108974098 | T/C | 1.06 (0.95-1.19) | 0.294 | 0.371 |
| rs2802292 | 8,9,13 | 6 | 108908518 | T/G | 1.01 (0.91-1.12) | 0.864 | 0.864 |
| rs9400239 | 11 | 6 | 108977663 | C/T | 1.06 (0.95-1.19) | 0.294 | 0.371 |

SNP, single nucleotide polymorphism

[a]Gene or nearest genes

[b]Multivariable model adjusts for study membership (CT or OS), age, BMI, physical activity, education, marital status, alcohol consumption, smoking behavior, history of age-related diseases, and first five principal components

[c]N=3380

Table 3.8: Associations of Significant Loci from Previous Studies with Survival to Age 90 in White Women, Continued

| SNP | References | Chromosome | Position | Count allele/ Reference allele | OR (95% CI)[b] n=3503 | Uncorrected *P* value | Corrected *P* value |
|---|---|---|---|---|---|---|---|
| rs3800231 | 11 | 6 | 108998266 | G/A | 1.07 (0.96-1.20) | 0.239 | 0.371 |
| rs479744 | 10,11 | 6 | 109020032 | G/T | 1.04 (0.92-1.19) | 0.519 | 0.559 |
| rs1935949 | 12 | 6 | 108999287 | G/A | 1.07 (0.96-1.20) | 0.239 | 0.371 |
| rs4946935 | 12 | 6 | 109000742 | G/A | 1.07 (0.96-1.20) | 0.243 | 0.371 |

SNP, single nucleotide polymorphism
[a]Gene or nearest genes
[b]Multivariable model adjusts for study membership (CT or OS), age, BMI, physical activity, education, marital status, alcohol consumption, smoking behavior, history of age-related diseases, and first five principal components
[c]N=3380

Table 3.9: Age-Adjusted SNP Associations with Survival to Age 85 in White Women

| SNP | OR (95% CI)[a] (n=8656) | Uncorrected *P*-value | Corrected *P*-value |
|---|---|---|---|
| rs2075650[b] | 1.14 (1.02-1.26) | 0.018 | 0.104 |
| rs7412[b] | 0.88 (0.76-1.02) | 0.082 | 0.229 |
| rs429358[b] | 1.17 (1.05-1.30) | 0.005 | 0.067 |
| rs4420638[b] | 1.14 (1.02-1.27) | 0.022 | 0.104 |
| rs2149954 | 0.93 (0.86-1.00) | 0.048 | 0.169 |
| rs10457180 | 0.96 (0.89-1.04) | 0.336 | 0.497 |
| rs2764264 | 0.97 (0.90-1.05) | 0.461 | 0.497 |
| rs13217795 | 0.96 (0.89-1.04) | 0.352 | 0.497 |
| rs2802292 | 0.97 (0.90-1.04) | 0.424 | 0.497 |
| rs9400239 | 0.96 (0.89-1.04) | 0.334 | 0.497 |
| rs3800231 | 0.97 (0.90-1.05) | 0.449 | 0.497 |
| rs479744 | 1.00 (0.92-1.09) | 0.963 | 0.963 |
| rs1935949 | 0.97 (0.90-1.05) | 0.438 | 0.497 |
| rs4946935 | 0.97 (0.90-1.05) | 0.419 | 0.497 |

[a]Model adjusts for age and first five principal components
[b]n=8395

Table 3.10: Age-Adjusted SNP Associations with Survival to Age 90 in White Women

| SNP | OR (95% CI)[a] (n=3870) | Uncorrected *P*-value | Corrected *P*-value |
|---|---|---|---|
| rs2075650[b] | 1.30 (1.13-1.50) | 0.0003 | 0.002 |
| rs7412[b] | 0.79 (0.67-0.95) | 0.011 | 0.038 |
| rs429358[b] | 1.40 (1.21-1.63) | <0.0001 | 0.001 |
| rs4420638[b] | 1.31 (1.13-1.52) | 0.0004 | 0.002 |
| rs2149954 | 0.96 (0.88-1.06) | 0.421 | 0.439 |
| rs10457180 | 1.07 (0.97-1.18) | 0.184 | 0.249 |
| rs2764264 | 1.08 (0.98-1.20) | 0.127 | 0.249 |
| rs13217795 | 1.07 (0.97-1.19) | 0.168 | 0.249 |
| rs2802292 | 1.05 (0.96-1.16) | 0.303 | 0.353 |
| rs9400239 | 1.07 (0.97-1.18) | 0.185 | 0.249 |
| rs3800231 | 1.07 (0.97-1.19) | 0.192 | 0.249 |
| rs479744 | 1.05 (0.93-1.17) | 0.439 | 0.439 |
| rs1935949 | 1.07 (0.97-1.18) | 0.192 | 0.249 |
| rs4946935 | 1.07 (0.97-1.18) | 0.196 | 0.249 |

[a]Model adjusts for age and first five principal components
[b]n=3736

Table 3.11: Associations of SNPs with Survival to Age 85 in African-American Women

| SNP | Chromosome | Position | Count allele/ Reference allele | OR (95% CI)[b] n=1685 | Uncorrected *P*-value | Corrected *P*-value |
|---|---|---|---|---|---|---|
| *TOMM40*[a] | | | | | | |
| rs2075650 | 19 | 45395619 | A/G | 1.25 (0.87-1.80) | 0.235 | 0.939 |
| *APOC1*[a] | | | | | | |
| rs4420638 | 19 | 45422946 | A/G | 1.23 (1.00-1.52) | 0.052 | 0.654 |
| *APOE*[a] | | | | | | |
| rs7412 | 19 | 45412079 | C/T | 1.00 (0.61-1.62) | 0.994 | 0.994 |
| rs429358 | 19 | 45411941 | T/C | 1.07 (0.80-1.44) | 0.656 | 0.946 |
| *CLINT1, EBF1*[a] | | | | | | |
| rs2149954 | 5 | 157820602 | C/T | 1.03 (0.88-1.22) | 0.692 | 0.946 |
| rs7721599 | 5 | 157819991 | C/T | 1.03 (0.88-1.22) | 0.699 | 0.946 |
| rs7724836 | 5 | 157826281 | G/A | 1.04 (0.88-1.22) | 0.675 | 0.946 |
| rs12187074 | 5 | 157811935 | C/G | 1.00 (0.85-1.18) | 0.971 | 0.994 |
| rs13163917 | 5 | 157832300 | A/G | 1.03 (0.88-1.22) | 0.708 | 0.946 |
| rs10476247 | 5 | 157856569 | A/T | 1.14 (0.96-1.34) | 0.134 | 0.654 |
| rs9313775 | 5 | 157856776 | G/A | 1.13 (0.96-1.34) | 0.139 | 0.654 |
| rs10044792 | 5 | 157861839 | C/T | 1.13 (0.96-1.34) | 0.138 | 0.654 |
| rs10037337 | 5 | 157862392 | T/G | 1.13 (0.96-1.34) | 0.140 | 0.654 |
| rs12716344 | 5 | 157876908 | C/G | 1.14 (0.97-1.35) | 0.114 | 0.654 |
| *FOXO3A*[a] | | | | | | |
| rs10457180 | 6 | 108965039 | A/G | 0.99 (0.80-1.22) | 0.925 | 0.994 |
| rs2764264 | 6 | 108934461 | T/C | 1.00 (0.81-1.22) | 0.962 | 0.994 |

SNP, single nucleotide polymorphism
[a]Gene or nearest genes
[b]Multivariable model adjusts for study membership (CT or OS), age, BMI, physical activity, education, marital status, alcohol consumption, smoking behavior, history of age-related diseases, and first five principal components

Table 3.11: Associations of SNPs with Survival to Age 85 in African-American Women, Continued

| SNP | Chromosome | Position | Count allele/ Reference allele | OR (95% CI)[b] n=1685 | Uncorrected *P*-value | Corrected *P*-value |
|---|---|---|---|---|---|---|
| rs13217795 | 6 | 108974098 | T/C | 0.99 (0.83-1.19) | 0.937 | 0.994 |
| rs4946932 | 6 | 108974746 | C/A | 1.01 (0.84-1.22) | 0.918 | 0.994 |
| rs4946935 | 6 | 109000742 | G/A | 0.95 (0.78-1.16) | 0.626 | 0.946 |
| rs4946936 | 6 | 109003321 | C/T | 0.96 (0.78-1.18) | 0.716 | 0.946 |
| rs2802288 | 6 | 108896215 | G/A | 1.10 (0.92-1.32) | 0.311 | 0.946 |
| rs2802292 | 6 | 108908518 | T/G | 1.09 (0.91-1.31) | 0.361 | 0.946 |
| rs9400239 | 6 | 108977663 | C/T | 1.03 (0.86-1.25) | 0.724 | 0.946 |
| rs2253310 | 6 | 108888593 | G/C | 1.10 (0.92-1.32) | 0.318 | 0.946 |
| rs3800231 | 6 | 108998266 | G/A | 0.96 (0.78-1.17) | 0.667 | 0.946 |
| rs479744 | 6 | 109020032 | G/T | 0.97 (0.83-1.14) | 0.743 | 0.946 |
| rs1935949 | 6 | 108999287 | G/A | 0.95 (0.78-1.16) | 0.633 | 0.946 |
| rs9398172 | 6 | 108994826 | A/G | 0.96 (0.79-1.17) | 0.704 | 0.946 |

SNP, single nucleotide polymorphism

[a]Gene or nearest genes

[b]Multivariable model adjusts for study membership (CT or OS), age, BMI, physical activity, education, marital status, alcohol consumption, smoking behavior, history of age-related diseases, and first five principal components

Table 3.12: Associations of SNPs with Survival to Age 90 in African-American Women

| SNP | Chromosome | Position | Count allele/ Reference allele | OR (95% CI)[b] n=644 | Uncorrected *P*-value | Corrected *P*-value |
|---|---|---|---|---|---|---|
| *TOMM40*[a] | | | | | | |
| rs2075650 | 19 | 45395619 | A/G | 1.29 (0.74-2.26) | 0.369 | 0.470 |
| *APOC1*[a] | | | | | | |
| rs4420638 | 19 | 45422946 | A/G | 1.20 (0.87-1.66) | 0.262 | 0.431 |
| *APOE*[a] | | | | | | |
| rs7412 | 19 | 45412079 | C/T | 0.62 (0.29-1.33) | 0.220 | 0.411 |
| rs429358 | 19 | 45411941 | T/C | 1.69 (1.07-2.69) | 0.026 | 0.334 |
| *CLINT1, EBF1*[a] | | | | | | |
| rs2149954 | 5 | 157820602 | C/T | 1.23 (0.96-1.58) | 0.108 | 0.334 |
| rs7721599 | 5 | 157819991 | C/T | 1.23 (0.96-1.58) | 0.109 | 0.334 |
| rs7724836 | 5 | 157826281 | G/A | 1.21 (0.95-1.56) | 0.129 | 0.334 |
| rs12187074 | 5 | 157811935 | C/G | 1.22 (0.95-1.57) | 0.122 | 0.334 |
| rs13163917 | 5 | 157832300 | A/G | 1.21 (0.94-1.56) | 0.131 | 0.334 |
| rs10476247 | 5 | 157856569 | A/T | 1.26 (0.97-1.63) | 0.079 | 0.334 |
| rs9313775 | 5 | 157856776 | G/A | 1.29 (0.99-1.66) | 0.057 | 0.334 |
| rs10044792 | 5 | 157861839 | C/T | 1.26 (0.97-1.63) | 0.079 | 0.334 |
| rs10037337 | 5 | 157862392 | T/G | 1.26 (0.97-1.63) | 0.080 | 0.334 |
| rs12716344 | 5 | 157876908 | C/G | 1.22 (0.95-1.57) | 0.128 | 0.334 |
| *FOXO3A*[a] | | | | | | |
| rs10457180 | 6 | 108965039 | A/G | 1.22 (0.88-1.68) | 0.240 | 0.419 |
| rs2764264 | 6 | 108934461 | T/C | 1.17 (0.86-1.60) | 0.326 | 0.468 |

SNP, single nucleotide polymorphism

[a]Gene or nearest genes

[b]Multivariable model adjusts for study membership (CT or OS), age, BMI, physical activity, education, marital status, alcohol consumption, smoking behavior, history of age-related diseases, and first five principal components

Table 3.12: Associations of SNPs with Survival to Age 90 in African-American Women, Continued

| SNP | Chromosome | Position | Count allele/ Reference allele | OR (95% CI)[b] n=644 | Uncorrected *P*-value | Corrected *P*-value |
|---|---|---|---|---|---|---|
| rs13217795 | 6 | 108974098 | T/C | 1.09 (0.83-1.43) | 0.520 | 0.520 |
| rs4946932 | 6 | 108974746 | C/A | 1.11 (0.84-1.47) | 0.453 | 0.478 |
| rs4946935 | 6 | 109000742 | G/A | 1.13 (0.82-1.55) | 0.460 | 0.478 |
| rs4946936 | 6 | 109003321 | C/T | 1.13 (0.82-1.56) | 0.449 | 0.478 |
| rs2802288 | 6 | 108896215 | G/A | 1.21 (0.92-1.61) | 0.176 | 0.387 |
| rs2802292 | 6 | 108908518 | T/G | 1.21 (0.91-1.61) | 0.186 | 0.387 |
| rs9400239 | 6 | 108977663 | C/T | 1.12 (0.85-1.49) | 0.421 | 0.478 |
| rs2253310 | 6 | 108888593 | G/C | 1.16 (0.88-1.54) | 0.287 | 0.446 |
| rs3800231 | 6 | 108998266 | G/A | 1.16 (0.85-1.60) | 0.351 | 0.468 |
| rs479744 | 6 | 109020032 | G/T | 1.19 (0.92-1.54) | 0.193 | 0.387 |
| rs1935949 | 6 | 108999287 | G/A | 1.14 (0.83-1.56) | 0.423 | 0.478 |
| rs9398172 | 6 | 108994826 | A/G | 1.16 (0.85-1.59) | 0.345 | 0.468 |

SNP, single nucleotide polymorphism

[a]Gene or nearest genes

[b]Multivariable model adjusts for study membership (CT or OS), age, BMI, physical activity, education, marital status, alcohol consumption, smoking behavior, history of age-related diseases, and first five principal components

Table 3.13: Age-Adjusted SNP Associations with Survival to Age 85 in African-American Women

| SNP | OR (95% CI)[a] (n=1858) | Uncorrected *P*-value | Corrected *P*-value |
|---|---|---|---|
| rs2075650 | 1.32 (0.97-1.80) | 0.081 | 0.930 |
| rs4420638 | 1.12 (0.94-1.34) | 0.206 | 0.930 |
| rs7412 | 0.90 (0.59-1.36) | 0.607 | 0.930 |
| rs429358 | 1.04 (0.81-1.34) | 0.754 | 0.930 |
| rs2149954 | 0.96 (0.83-1.10) | 0.528 | 0.930 |
| rs7721599 | 0.95 (0.83-1.10) | 0.515 | 0.930 |
| rs7724836 | 0.97 (0.84-1.12) | 0.668 | 0.930 |
| rs12187074 | 0.93 (0.81-1.07) | 0.326 | 0.930 |
| rs13163917 | 0.97 (0.85-1.12) | 0.706 | 0.930 |
| rs10476247 | 1.06 (0.92-1.22) | 0.420 | 0.930 |
| rs9313775 | 1.05 (0.91-1.22) | 0.472 | 0.930 |
| rs10044792 | 1.06 (0.92-1.22) | 0.455 | 0.930 |
| rs10037337 | 1.06 (0.92-1.22) | 0.454 | 0.930 |
| rs12716344 | 1.06 (0.92-1.22) | 0.452 | 0.930 |
| rs10457180 | 0.99 (0.82-1.19) | 0.928 | 0.988 |
| rs2764264 | 0.98 (0.82-1.17) | 0.833 | 0.971 |
| rs13217795 | 0.97 (0.83-1.14) | 0.734 | 0.930 |
| rs4946932 | 1.00 (0.85-1.17) | 0.988 | 0.988 |
| rs4946935 | 0.95 (0.79-1.13) | 0.523 | 0.930 |
| rs4946936 | 0.96 (0.80-1.15) | 0.657 | 0.930 |
| rs2802288 | 1.03 (0.88-1.21) | 0.688 | 0.930 |
| rs2802292 | 1.02 (0.88-1.20) | 0.764 | 0.930 |
| rs9400239 | 1.00 (0.86-1.18) | 0.957 | 0.988 |
| rs2253310 | 1.04 (0.89-1.21) | 0.665 | 0.930 |
| rs3800231 | 0.95 (0.80-1.13) | 0.569 | 0.930 |
| rs479744 | 1.00 (0.87-1.15) | 0.964 | 0.988 |
| rs1935949 | 0.95 (0.80-1.13) | 0.560 | 0.930 |
| rs9398172 | 0.96 (0.81-1.14) | 0.633 | 0.930 |

[a]Adjusted for age and first five principal components

Table 3.14: Age-Adjusted SNP Associations with Survival to Age 90 in African-American Women

| SNP | OR (95% CI)[a] (n=726) | Uncorrected *P*-value | Corrected *P*-value |
|---|---|---|---|
| rs2075650 | 1.27 (0.79-2.02) | 0.322 | 0.441 |
| rs4420638 | 1.05 (0.80-1.37) | 0.726 | 0.726 |
| rs7412 | 0.62 (0.33-1.18) | 0.147 | 0.441 |
| rs429358 | 1.42 (0.96-2.11) | 0.079 | 0.441 |
| rs2149954 | 1.09 (0.88-1.35) | 0.440 | 0.458 |
| rs7721599 | 1.09 (0.88-1.35) | 0.441 | 0.458 |
| rs7724836 | 1.10 (0.89-1.36) | 0.378 | 0.441 |
| rs12187074 | 1.09 (0.88-1.35) | 0.438 | 0.458 |
| rs13163917 | 1.11 (0.89-1.37) | 0.361 | 0.441 |
| rs10476247 | 1.14 (0.92-1.42) | 0.244 | 0.441 |
| rs9313775 | 1.15 (0.92-1.43) | 0.215 | 0.441 |
| rs10044792 | 1.14 (0.92-1.42) | 0.243 | 0.441 |
| rs10037337 | 1.14 (0.92-1.42) | 0.242 | 0.441 |
| rs12716344 | 1.11 (0.90-1.38) | 0.331 | 0.441 |
| rs10457180 | 1.21 (0.92-1.59) | 0.171 | 0.441 |
| rs2764264 | 1.15 (0.88-1.50) | 0.299 | 0.441 |
| rs13217795 | 1.11 (0.88-1.40) | 0.378 | 0.441 |
| rs4946932 | 1.15 (0.91-1.45) | 0.256 | 0.441 |
| rs4946935 | 1.13 (0.87-1.48) | 0.361 | 0.441 |
| rs4946936 | 1.13 (0.86-1.48) | 0.374 | 0.441 |
| rs2802288 | 1.19 (0.94-1.51) | 0.153 | 0.441 |
| rs2802292 | 1.18 (0.93-1.50) | 0.168 | 0.441 |
| rs9400239 | 1.15 (0.90-1.45) | 0.259 | 0.441 |
| rs2253310 | 1.17 (0.92-1.48) | 0.195 | 0.441 |
| rs3800231 | 1.15 (0.88-1.51) | 0.300 | 0.441 |
| rs479744 | 1.14 (0.92-1.41) | 0.243 | 0.441 |
| rs1935949 | 1.14 (0.87-1.48) | 0.343 | 0.441 |
| rs9398172 | 1.16 (0.89-1.51) | 0.278 | 0.441 |

[a]Model adjusted for age and first five principal components

Table 3.15: Associations of SNPs with Survival to Age 85 in Hispanic Women

| SNP | Chromosome | Position | Count allele/ Reference allele | OR (95% CI)[b] n=474 | Uncorrected *P*-value | Corrected *P*-value |
|---|---|---|---|---|---|---|
| *TOMM40*[a] | | | | | | |
| rs2075650 | 19 | 45395619 | A/G | 1.86 (0.84-4.10) | 0.125 | 0.353 |
| *APOC1*[a] | | | | | | |
| rs4420638 | 19 | 45422946 | A/G | 1.00 (0.58-1.72) | 0.999 | 0.999 |
| *APOE*[a] | | | | | | |
| rs7412 | 19 | 45412079 | C/T | 0.77 (0.21-2.90) | 0.700 | 0.812 |
| rs429358 | 19 | 45411941 | T/C | 1.13 (0.58-2.18) | 0.724 | 0.812 |
| *CLINT1, EBF1*[a] | | | | | | |
| rs2149954 | 5 | 157820602 | C/T | 1.41 (0.99-2.02) | 0.060 | 0.207 |
| rs7721599 | 5 | 157819991 | C/T | 1.41 (0.99-2.02) | 0.060 | 0.207 |
| rs7724836 | 5 | 157826281 | G/A | 1.56 (1.10-2.22) | 0.015 | 0.191 |
| rs4704775 | 5 | 157824556 | G/A | 1.29 (0.89-1.85) | 0.175 | 0.452 |
| rs7701003 | 5 | 157824481 | A/G | 1.35 (0.96-1.92) | 0.089 | 0.277 |
| rs13163917 | 5 | 157832300 | A/G | 1.56 (1.09-2.22) | 0.015 | 0.191 |
| rs17694395 | 5 | 157851580 | C/T | 1.46 (1.02-2.09) | 0.037 | 0.191 |
| rs9313775 | 5 | 157856776 | G/A | 1.44 (1.01-2.06) | 0.046 | 0.202 |
| rs10044792 | 5 | 157861839 | C/T | 1.46 (1.02-2.09) | 0.037 | 0.191 |
| rs10037337 | 5 | 157862392 | T/G | 1.46 (1.02-2.09) | 0.036 | 0.191 |
| rs12716344 | 5 | 157876908 | C/G | 1.53 (1.07-2.19) | 0.021 | 0.191 |
| *FOXO3A*[a] | | | | | | |
| rs10457180 | 6 | 108965039 | A/G | 1.08 (0.77-1.52) | 0.673 | 0.812 |
| rs2764264 | 6 | 108934461 | T/C | 1.06 (0.75-1.49) | 0.751 | 0.812 |

SNP, single nucleotide polymorphism

[a]Gene or nearest genes

[b]Multivariable model adjusts for study membership (CT or OS), age, BMI, physical activity, education, marital status, alcohol consumption, smoking behavior, history of age-related diseases, and first five principal components

Table 3.15: Associations of SNPs with Survival to Age 85 in Hispanic Women, Continued

| SNP | Chromosome | Position | Count allele/ Reference allele | OR (95% CI)[b] n=474 | Uncorrected *P*-value | Corrected *P*-value |
|---|---|---|---|---|---|---|
| rs13217795 | 6 | 108974098 | T/C | 1.15 (0.82-1.62) | 0.415 | 0.812 |
| rs4946932 | 6 | 108974746 | C/A | 1.15 (0.82-1.62) | 0.422 | 0.812 |
| rs4946935 | 6 | 109000742 | G/A | 1.07 (0.76-1.51) | 0.701 | 0.812 |
| rs4946936 | 6 | 109003321 | C/T | 1.10 (0.78-1.56) | 0.579 | 0.812 |
| rs2802292 | 6 | 108908518 | T/G | 1.05 (0.75-1.46) | 0.786 | 0.812 |
| rs9400239 | 6 | 108977663 | C/T | 1.15 (0.82-1.62) | 0.421 | 0.812 |
| rs479744 | 6 | 109020032 | G/T | 1.07 (0.74-1.54) | 0.712 | 0.812 |
| rs1935949 | 6 | 108999287 | G/A | 1.07 (0.76-1.51) | 0.699 | 0.812 |
| r1268164 | 6 | 109008416 | A/G | 1.05 (0.75-1.49) | 0.773 | 0.812 |
| rs1268165 | 6 | 109008378 | T/C | 1.05 (0.75-1.49) | 0.772 | 0.812 |
| rs1268167 | 6 | 109008183 | G/A | 1.05 (0.75-1.49) | 0.772 | 0.812 |
| rs1268169 | 6 | 109007977 | T/G | 1.05 (0.75-1.49) | 0.774 | 0.812 |
| rs3800231 | 6 | 108998266 | G/A | 1.07 (0.76-1.52) | 0.692 | 0.812 |
| rs9398172 | 6 | 108994826 | A/G | 1.07 (0.76-1.51) | 0.700 | 0.812 |

SNP, single nucleotide polymorphism

[a]Gene or nearest genes

[b]Multivariable model adjusts for study membership (CT or OS), age, BMI, physical activity, education, marital status, alcohol consumption, smoking behavior, history of age-related diseases, and first five principal components

Table 3.16: Age-Adjusted SNP Associations with Survival to Age 85 in Hispanic Women

| SNP | OR (95% CI)[a] (n=539) | Uncorrected *P*-value | Corrected *P*-value |
|---|---|---|---|
| rs2075650 | 1.88 (1.00-3.54) | 0.050 | 0.141 |
| rs7412 | 0.83 (0.27-2.58) | 0.746 | 0.746 |
| rs429358 | 1.32 (0.78-2.23) | 0.310 | 0.563 |
| rs4420638 | 1.08 (0.70-1.68) | 0.719 | 0.743 |
| rs2149954 | 1.44 (1.07-1.93) | 0.015 | 0.053 |
| rs7721599 | 1.44 (1.07-1.93) | 0.015 | 0.053 |
| rs7724836 | 1.57 (1.17-2.09) | 0.002 | 0.037 |
| rs4704775 | 1.25 (0.93-1.69) | 0.142 | 0.368 |
| rs7701003 | 1.40 (1.05-1.87) | 0.022 | 0.070 |
| rs13163917 | 1.56 (1.17-2.09) | 0.002 | 0.037 |
| rs17694395 | 1.49 (1.11-1.99) | 0.007 | 0.037 |
| rs9313775 | 1.48 (1.10-1.98) | 0.008 | 0.037 |
| rs10044792 | 1.49 (1.11-1.99) | 0.007 | 0.037 |
| rs10037337 | 1.49 (1.11-1.99) | 0.007 | 0.037 |
| rs12716344 | 1.53 (1.14-2.04) | 0.005 | 0.037 |
| rs10457180 | 1.11 (0.83-1.48) | 0.478 | 0.565 |
| rs2764264 | 1.09 (0.82-1.46) | 0.555 | 0.588 |
| rs13217795 | 1.15 (0.87-1.53) | 0.337 | 0.563 |
| rs4946932 | 1.15 (0.86-1.52) | 0.351 | 0.563 |
| rs4946935 | 1.14 (0.85-1.52) | 0.378 | 0.563 |
| rs4946936 | 1.16 (0.87-1.55) | 0.317 | 0.563 |
| rs2802292 | 1.11 (0.84-1.46) | 0.469 | 0.565 |
| rs9400239 | 1.15 (0.86-1.52) | 0.346 | 0.563 |
| rs479744 | 1.11 (0.82-1.50) | 0.510 | 0.565 |
| rs1935949 | 1.14 (0.85-1.52) | 0.376 | 0.563 |
| r1268164 | 1.10 (0.83-1.47) | 0.500 | 0.565 |
| rs1268165 | 1.10 (0.83-1.47) | 0.499 | 0.565 |
| rs1268167 | 1.10 (0.83-1.47) | 0.499 | 0.565 |
| rs1268169 | 1.10 (0.83-1.47) | 0.500 | 0.565 |
| rs3800231 | 1.14 (0.85-1.52) | 0.381 | 0.563 |
| rs9398172 | 1.14 (0.85-1.52) | 0.377 | 0.563 |

[a]Model adjusts for age and first five principal components

Table 3.17: Associations of SNPs with Healthy Aging in White Women

| SNP | Chromosome | Position | Count allele/ Reference allele | OR (95% CI) Healthy survival vs. Died before 85[b] n=4673 | OR (95% CI) Usual survival vs. Died before 85[b] n=4673 | Uncorrected *P*-value | Corrected *P*-value |
|---|---|---|---|---|---|---|---|
| *TOMM40*[a] | | | | | | | |
| rs2075650 | 19 | 45395619 | A/G | 1.21 (1.03-1.43)[c] | 1.19 (1.02-1.38)[c] | 0.027 | 0.094 |
| *APOC1*[a] | | | | | | | |
| rs4420638 | 19 | 45422946 | A/G | 1.28 (1.08-1.52)[c] | 1.25 (1.07-1.46)[c] | 0.003 | 0.021 |
| *APOE*[a] | | | | | | | |
| rs7412 | 19 | 45412079 | C/T | 0.86 (0.69-1.06)[c] | 0.87 (0.71-1.05)[c] | 0.236 | 0.661 |
| rs429358 | 19 | 45411941 | T/C | 1.32 (1.11-1.57)[c] | 1.26 (1.08-1.48)[c] | 0.002 | 0.021 |
| *CLINT1, EBF1*[a] | | | | | | | |
| rs2149954 | 5 | 157820602 | C/T | 0.97 (0.86-1.08) | 0.87 (0.79-0.96) | 0.021 | 0.094 |
| *FOXO3A*[a] | | | | | | | |
| rs10457180 | 6 | 108965039 | A/G | 0.99 (0.87-1.11) | 1.00 (0.90-1.11) | 0.970 | 0.975 |
| rs2764264 | 6 | 108934461 | T/C | 1.00 (0.88-1.13) | 1.01 (0.91-1.12) | 0.975 | 0.975 |
| rs13217795 | 6 | 108974098 | T/C | 0.98 (0.87-1.11) | 1.01 (0.90-1.12) | 0.930 | 0.975 |
| rs2802292 | 6 | 108908518 | T/G | 0.96 (0.86-1.08) | 0.97 (0.88-1.08) | 0.776 | 0.975 |
| rs9400239 | 6 | 108977663 | C/T | 0.99 (0.88-1.11) | 1.00 (0.90-1.12) | 0.959 | 0.975 |

[a]Gene or nearest genes
[b]Multivariable model adjusts for study membership (CT or OS), age, BMI, physical activity, education, marital status, alcohol consumption, smoking behavior, and first five principal components
[c]N=4517

Table 3.17: Associations of SNPs with Healthy Aging in White Women, Continued

| SNP | Chromosome | Position | Count allele/ Reference allele | OR (95% CI) Healthy survival vs. Died before 85[b] n=4673 | OR (95% CI) Usual survival vs. Died before 85[b] n=4673 | Uncorrected *P*-value | Corrected *P*-value |
|---|---|---|---|---|---|---|---|
| rs3800231 | 6 | 108998266 | G/A | 1.01 (0.89-1.14) | 1.02 (0.92-1.14) | 0.922 | 0.975 |
| rs479744 | 6 | 109020032 | G/T | 1.07 (0.93-1.22) | 1.02 (0.91-1.15) | 0.651 | 0.975 |
| rs1935949 | 6 | 108999287 | G/A | 1.01 (0.89-1.14) | 1.02 (0.92-1.13) | 0.947 | 0.975 |
| rs4946935 | 6 | 109000742 | G/A | 1.01 (0.89-1.14) | 1.02 (0.91-1.13) | 0.948 | 0.975 |

[a]Gene or nearest genes
[b]Multivariable model adjusts for study membership (CT or OS), age, BMI, physical activity, education, marital status, alcohol consumption, smoking behavior, and first five principal components
[c]N=4517

Table 3.18: Age-Adjusted SNP Associations with Healthy Survival to Age 85 in White Women

| SNP | OR (95% CI)[a] Healthy survival vs. Died before 85 (n=5092) | OR (95% CI)[a] Usual survival vs. Died before 85 (n=5092) | Uncorrected *P*-value | Corrected *P*-value |
|---|---|---|---|---|
| rs2075650[b] | 1.19 (1.02-1.39) | 1.17 (1.02-1.35) | 0.028 | 0.128 |
| rs7412[b] | 0.84 (0.69-1.02) | 0.86 (0.72-1.03) | 0.135 | 0.379 |
| rs429358[b] | 1.31 (1.11-1.54) | 1.27 (1.10-1.47) | 0.0005 | 0.007 |
| rs4420638[b] | 1.26 (1.08-1.48) | 1.26 (1.09-1.46) | 0.001 | 0.010 |
| rs2149954 | 0.97 (0.87-1.08) | 0.89 (0.81-0.98) | 0.051 | 0.177 |
| rs10457180 | 0.97 (0.87-1.08) | 1.00 (0.90-1.10) | 0.856 | 0.968 |
| rs2764264 | 0.98 (0.88-1.10) | 1.01 (0.91-1.12) | 0.906 | 0.968 |
| rs13217795 | 0.97 (0.87-1.08) | 1.01 (0.91-1.11) | 0.796 | 0.968 |
| rs2802292 | 0.98 (0.88-1.08) | 1.00 (0.91-1.10) | 0.890 | 0.968 |
| rs9400239 | 0.97 (0.87-1.08) | 1.00 (0.91-1.11) | 0.834 | 0.968 |
| rs3800231 | 0.99 (0.88-1.10) | 1.01 (0.92-1.12) | 0.917 | 0.968 |
| rs479744 | 1.02 (0.90-1.15) | 1.01 (0.90-1.13) | 0.968 | 0.968 |
| rs1935949 | 0.99 (0.88-1.10) | 1.01 (0.91-1.12) | 0.925 | 0.968 |
| rs4946935 | 0.98 (0.88-1.10) | 1.01 (0.91-1.12) | 0.917 | 0.968 |

[a]Adjusted for age and first five principal components
[b]n=4927

Table 3.19: Estimated Power to Detect Effect Sizes in White Women for Survival to Age 85

| Allele Frequency | Odds Ratio | Power (%) |
|---|---|---|
| 0.05 | 1.25 | 82.7 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.10 | 1.25 | 97.8 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.15 | 1.25 | 99.9 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.20 | 1.25 | 99.9 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.25 | 1.25 | 99.9 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.30 | 1.25 | 99.9 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.35 | 1.25 | 99.9 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.40 | 1.25 | 99.9 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |

Assumptions: 6477 survivors to age 85, 2179 died before age 85, gene-only model, disease trait phenotype (i.e, survival), additive genetic model, 2% likelihood of reaching age 85 or above, 5% type I error rate, and two-sided hypothesis test.

Table 3.20: Estimated Power to Detect Effect Sizes in White Women for Survival to Age 90

| Allele Frequency | Odds Ratio | Power (%) |
|---|---|---|
| 0.05 | 1.25 | 61.0 |
| | 1.50 | 98.8 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.10 | 1.25 | 86.5 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.15 | 1.25 | 95.2 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.20 | 1.25 | 98.1 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.25 | 1.25 | 99.2 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.30 | 1.25 | 99.6 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.35 | 1.25 | 99.7 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.40 | 1.25 | 99.8 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |

Assumptions: 2059 survivors to age 90, 1811 died before age 90, gene-only model, disease trait phenotype (i.e, survival), additive genetic model, 1% likelihood of reaching age 90 or above, 5% type I error rate, and two-sided hypothesis test.

Table 3.21: Estimated Power to Detect Effect Sizes in White Women for Healthy Aging

| Allele Frequency | Odds Ratio | Power (%) |
|---|---|---|
| 0.05 | 1.25 | 52.3 |
| | 1.50 | 96.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.10 | 1.25 | 78.7 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.15 | 1.25 | 90.3 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.20 | 1.25 | 95.3 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.25 | 1.25 | 97.4 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.30 | 1.25 | 98.4 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.35 | 1.25 | 98.9 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.40 | 1.25 | 99.1 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |

Assumptions: 1202 healthy survivors to age 85, 2179 died before age 85, gene-only model, disease trait phenotype (i.e, survival), additive genetic model, 1% likelihood of achieving healthy aging, 5% type I error rate, and two-sided hypothesis test.

Table 3.22: Estimated Power to Detect Effect Sizes in African-American Women for Survival to Age 85

| Allele Frequency | Odds Ratio | Power (%) |
|---|---|---|
| 0.05 | 1.25 | 31.3 |
| | 1.50 | 79.0 |
| | 1.75 | 97.6 |
| | 2.00 | 99.9 |
| 0.10 | 1.25 | 52.2 |
| | 1.50 | 96.5 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.15 | 1.25 | 66.5 |
| | 1.50 | 99.3 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.20 | 1.25 | 75.7 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.25 | 1.25 | 81.7 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.30 | 1.25 | 85.4 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.35 | 1.25 | 87.7 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.40 | 1.25 | 89.1 |
| | 1.50 | 99.9 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |

Assumptions: 1211 survivors to age 85, 647 died before age 85, gene-only model, disease trait phenotype (i.e, survival), additive genetic model, 2% likelihood of reaching age 85 or above, 5% type I error rate, and two-sided hypothesis test.

Table 3.23: Estimated Power to Detect Effect Sizes in African-American Women for Survival to Age 90

| Allele Frequency | Odds Ratio | Power (%) |
|---|---|---|
| 0.05 | 1.25 | 16.2 |
| | 1.50 | 44.8 |
| | 1.75 | 74.1 |
| | 2.00 | 91.3 |
| 0.10 | 1.25 | 26.3 |
| | 1.50 | 70.2 |
| | 1.75 | 94.1 |
| | 2.00 | 99.4 |
| 0.15 | 1.25 | 34.8 |
| | 1.50 | 83.3 |
| | 1.75 | 98.5 |
| | 2.00 | 99.9 |
| 0.20 | 1.25 | 41.5 |
| | 1.50 | 90.0 |
| | 1.75 | 99.5 |
| | 2.00 | 99.9 |
| 0.25 | 1.25 | 46.8 |
| | 1.50 | 93.5 |
| | 1.75 | 99.8 |
| | 2.00 | 99.9 |
| 0.30 | 1.25 | 50.7 |
| | 1.50 | 95.3 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.35 | 1.25 | 53.4 |
| | 1.50 | 96.3 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |
| 0.40 | 1.25 | 55.1 |
| | 1.50 | 96.7 |
| | 1.75 | 99.9 |
| | 2.00 | 99.9 |

Assumptions: 343 survivors to age 90, 383 died before age 90, gene-only model, disease trait phenotype (i.e, survival), additive genetic model, 1% likelihood of reaching age 90 or above, 5% type I error rate, and two-sided hypothesis test.

Table 3.24: Estimated Power to Detect Effect Sizes in Hispanic Women for Survival to Age 85

| Allele Frequency | Odds Ratio | Power (%) |
|---|---|---|
| 0.05 | 1.25 | 11.5 |
| | 1.50 | 28.6 |
| | 1.75 | 50.7 |
| | 2.00 | 70.8 |
| 0.10 | 1.25 | 17.4 |
| | 1.50 | 47.7 |
| | 1.75 | 76.5 |
| | 2.00 | 92.3 |
| 0.15 | 1.25 | 22.6 |
| | 1.50 | 61.1 |
| | 1.75 | 88.3 |
| | 2.00 | 97.7 |
| 0.20 | 1.25 | 26.9 |
| | 1.50 | 70.1 |
| | 1.75 | 93.6 |
| | 2.00 | 99.2 |
| 0.25 | 1.25 | 30.4 |
| | 1.50 | 76.0 |
| | 1.75 | 96.1 |
| | 2.00 | 99.6 |
| 0.30 | 1.25 | 33.2 |
| | 1.50 | 79.9 |
| | 1.75 | 97.3 |
| | 2.00 | 99.8 |
| 0.35 | 1.25 | 35.2 |
| | 1.50 | 82.3 |
| | 1.75 | 97.9 |
| | 2.00 | 99.9 |
| 0.40 | 1.25 | 36.5 |
| | 1.50 | 83.6 |
| | 1.75 | 98.2 |
| | 2.00 | 99.9 |

Assumptions: 390 survivors to age 85, 149 died before age 85, gene-only model, disease trait phenotype (i.e, survival), additive genetic model, 2% likelihood of reaching age 85 or above, 5% type I error rate, and two-sided hypothesis test.

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# CHAPTER 4: ASSOCIATION OF ACCELEROMETER-MEASURED AND SELF-REPORTED SEDENTARY TIME WITH LEUKOCYTE TELOMERE LENGTH IN OLDER WOMEN

**Abstract**

**Background**: Epidemiological studies have observed associations between leukocyte telomere length (LTL) and health indices in adults. However, few studies have comprehensively assessed the association of sedentary time with LTL.

**Methods**: In this cross-sectional study, we examined the associations of accelerometer-measured and self-reported sedentary time with LTL in a sample of 1,481 older white and African American women from the Women's Health Initiative Objective Physical Activity and Cardiovascular Health Study and also determined whether associations varied by level of moderate-to-vigorous intensity physical activity (MVPA). The association between sedentary time and LTL was evaluated using multiple linear regression models adjusted for demographic characteristics, lifestyle behaviors, health-related variables, and wear time in models for accelerometer-measured sedentary time.

**Results**: Women were on average aged 79.2 (standard deviation 6.7) years old. Self-reported sedentary time was not associated with LTL in the analyses. In a model adjusting for age, race/ethnicity, education, marital status, smoking, alcohol, body mass index, history of chronic diseases, and hormone therapy use, among women at or below the median level of accelerometer-measured MVPA, those in the highest quartile of accelerometer-measured sedentary time had significantly shorter LTL than those who were least sedentary, with an average difference of 170 (95% confidence interval 4-340) base pairs. Accelerometer-measured sedentary time was not associated with LTL in those above the median level of MVPA.

**Conclusions**: Findings suggest that, when based on accelerometer measurements, higher sedentary time may be associated with shorter LTL among less physically active women.

## Introduction

Telomeres are repetitive DNA-protein structures located at the end of chromosomes that protect and maintain chromosomal stability and integrity.[1] Telomeres progressively shorten with age, leading to cellular senescence and apoptosis.[2,3] Shortened leukocyte telomere length (LTL) has been associated with cardiovascular disease, type 2 diabetes, and major cancers.[3-6]

Emerging evidence has linked LTL to modifiable factors such as smoking, body mass index (BMI), and physical activity.[7-12] Sedentary behavior has also been studied in relation to LTL, but with mixed findings. In the Nurses' Health Study, there was no association of total sedentary time or specific sedentary behaviors with LTL[12], but in two recent studies, reduced sedentary time was associated with longer LTL.[13,14] However, these studies were limited by several factors, including failure to measure sedentary time objectively, i.e., by accelerometer. Accelerometer-measured sedentary time is not highly correlated with self-reported time, the latter of which often underestimates actual time spent in sedentary behaviors.[15] These studies also did not measure LTL using the Southern blot method, which has been shown to have low measurement error.[16,17] Additionally, they did not determine whether associations of sedentary time with LTL varied by level of physical activity. In previous studies, associations of sedentary time with adverse health outcomes have been stronger among those with low levels of physical activity.[18-21]

In the present cross-sectional study, we assessed associations of accelerometer-measured and self-reported sedentary time with LTL in older white and African American women from the Objective Physical Activity and Cardiovascular Health

(OPACH) Study, an ancillary study of the Women's Health Initiative (WHI). We also determined whether associations varied by hours of moderate-to-vigorous intensity physical activity (MVPA), race/ethnicity, and physical function. Understanding the relationship between sedentary time and LTL, a purported biomarker of cellular aging[22], is important among older adults, who spend 8.5-10.7 hours/day sedentary and are particularly vulnerable to the adverse health consequences (e.g., obesity, type 2 diabetes, and all-cause mortality) associated with prolonged sedentary time.[19,23-25]

## Methods

### Study Population and Data Collection

The WHI is a large, prospective study investigating major determinants of chronic diseases in postmenopausal women. Details of the study have been previously described.[26,27] Briefly, a racially and ethnically diverse cohort of 161,808 postmenopausal women aged 50 to 79 years old was recruited from 40 clinical centers nationwide during 1993-1998. Women were randomized into one or more of three clinical trials (CT), including one of two hormone therapy (HT) trials, or an observational study (OS). In 2005, 77% of eligible women agreed to be followed through 2010 in the first Extension Study (ES). In 2010, 87% of women consented to an additional five years of follow-up in the second ES. Over 7,800 women from the second ES were enrolled into the Long Life Study (LLS), which consisted of a one-time in-person visit conducted between March 2012 and May 2013. The population of the current study consisted of women from the OPACH study, an ancillary study of the LLS that enrolled 7,048 women.

At the 1993-1998 baseline examination, participants completed self-administered questionnaires assessing demographic characteristics, medical history, and lifestyle behaviors. The 2012-2013 visit involved collection of a blood sample and assessment of physical measurements (blood pressure, height, and weight) and physical functioning status. OPACH participants additionally wore an accelerometer for one week and completed a sleep log and physical activity questionnaire. A random sample of women from the LLS was selected for participation in a case-cohort study on the relationship between LTL and coronary heart disease (CHD). The present study was exclusive to women with LTL measurements and complete information on either accelerometer-measured (n=1,297) or self-reported (n=1,383) sedentary time, leaving 1,481 women in the final analytic sample.

All participants provided written informed consent, and Institutional Review Board approval was received by all participating institutions.

Accelerometer-Measured Variables

Participants were asked to wear a triaxial accelerometer (ActiGraph GT3X+; Pensacola, Florida) on their right hip for seven consecutive days during waking and sleeping hours except during bathing or swimming. Movement was captured along three axes (vertical, anteroposterior, and mediolateral) in 15-second epochs, and activity counts were provided as composite vector magnitudes (VM) of these three axes. Accelerometer wear time was identified using sleep logs and a computer-automated algorithm developed specifically for this study.[28] Non-wear time was defined as an interval of ≥90 minutes of consecutive zero VM counts/minute, with allowance of up to two minutes of nonzero VM counts if no counts were detected 30 minutes upstream or downstream from that interval;

any other non-zero VM counts were considered wear time.[29,30] Only participants with 4-7 valid days of accelerometer data were included in the analysis, with a valid day defined as having ≥10 hours of wear time.[31]

A calibration study was performed in 200 OPACH participants to determine relevant cutpoints along the distribution of VM counts to define sedentary behavior and physical activity intensity in older women.[32] Based on this study, sedentary behavior was defined as 0-18 VM counts/15 seconds and MVPA as ≥519 counts/15-seconds. Data are presented as the average number of hours spent per day in each of these behaviors. For example, hours/day of sedentary time was calculated as the sum of total sedentary time during all valid days divided by the number of valid days.

Self-Reported Variables

In the physical activity questionnaire, participants were asked to estimate time spent sitting in response to the question: *During a usual day and night, about how many hours do you spend sitting? Be sure to include the time you spend sitting at work, sitting at the table eating, driving or riding in a car or bus, and sitting up watching TV or talking.* Participants also estimated the time spent lying down: *During a usual day and night, about how many hours do you spend sleeping or lying down with your feet up? Be sure to include the time you spend sleeping or trying to sleep at night, resting or napping, and lying down watching TV*. A third question asked participants to estimate the number of hours typically spent sleeping per night during the past four weeks. Total daily sedentary time was calculated as the sum of sitting time and lying time minus sleeping time. This questionnaire previously showed moderate to high test-retest reliability.[33]

Participants also completed the Community Healthy Activities Model Program for Seniors (CHAMPS) physical activity questionnaire, which was developed specifically for older adults and measures time spent in domestic and leisure-time activities in a typical week during the past four weeks.[34] Data are presented as average hours/day spent in activities of moderate-to-vigorous intensity calculated by summing the total number of hours spent in these activities during a typical week then dividing by seven.

Covariates

In this study, variables assessed at the WHI baseline visit, at the 2012-2013 visit, and during WHI follow-up were used as covariates. Covariates collected at baseline included race/ethnicity, education, marital status, smoking status, and alcohol consumption. At the 2012-2013 visit, trained clinic staff measured height and weight and systolic and diastolic blood pressures. BMI was calculated as weight in kilograms divided by height in meters squared, and categorized according to standard cutpoints.[35] Current physical functioning status was measured objectively at the 2012-2013 visit using the Established Populations for Epidemiologic Studies of the Elderly (EPESE) Short Physical Performance Battery (SPPB), which provides a summary score (range 0-12) calculated as the sum of balance, chair stand, and gait speed scores, with a higher score indicating better physical performance.[36,37]

Variables assessed during WHI follow-up included self-rated health and a history of HT use, hypertension, and chronic diseases. Self-rated health was measured by the RAND 36-item short form survey[38]; the most recent value collected within two years of the 2012-2013 visit was used. History of HT use was defined according to self-reported use or participation in the HT trials. History of hypertension was defined as self-reported

physician diagnosis of hypertension, or use of antihypertensive medications, or systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg (measured during baseline, follow-up, or at the 2012-2013 visit). History of chronic diseases was defined as occurrence of one or more of the following diseases, each of which has been associated with both sedentary time and LTL in previous studies[4-6,21,39,40]: CHD, stroke, diabetes, and cancer (excluding non-melanoma skin cancer). Disease status was self-reported at baseline, and incident diseases were identified through the date of the 2012-2013 visit via periodic clinic visits and mailed questionnaires conducted biannually for CT participants and annually for OS and ES participants. Incident diseases except for diabetes were adjudicated by physician medical record review.[41] Diabetes was defined as self-reported physician diagnosis of diabetes treated with either oral medication or insulin.[42]

Measurement of LTL

DNA samples were extracted by the 5-prime method (5 PRIME, Inc.; Gaithersburg, MD) and sent in batches over a one-year period to the Center of Human Development and Aging Laboratory at Rutgers University for LTL measurement. Each batch consisted of randomly selected samples. The laboratory performing the LTL measurements was blinded to all participant characteristics. Quality control procedures included assessment of DNA integrity prior to LTL measurement.[16] DNA integrity was assessed visually after ethidium bromide-stained 1% agarose gel electrophoresis (200 V for 2 hours), and required that DNA appear as a single compact crown-shaped band migrating in parallel with the other samples on the gel. Telomere length in kilobases (kb) was determined by the mean length of the terminal restriction fragments using the Southern blot method, as previously described.[16] Each sample was run in duplicate on

different gels, and mean LTL was used in the analyses. The average inter-assay coefficient of variation for blinded pair sets was 2.0%.

Statistical Analysis

Accelerometer-measured and self-reported sedentary time variables were divided into quartiles for the analysis. Categorical variables were compared across quartiles of sedentary time using $\chi^2$ tests. Analysis of variance and Kruskal-Wallis tests were used for comparisons of normally distributed and non-normally distributed continuous variables across quartiles of sedentary time, respectively. As LTL was normally distributed, general linear models were used to determine age- and race/ethnicity-adjusted mean LTL values across quartiles of sedentary time. General linear models were also used to determine means of accelerometer-measured sedentary time and MVPA adjusted for average wear time (in hours/day).

Associations of accelerometer-measured and self-reported sedentary time with LTL were evaluated using multiple linear regression models. The first model adjusted for age and race/ethnicity, and successive models adjusted for other potential confounders including demographic characteristics (education and marital status), lifestyle behaviors (smoking, alcohol, BMI, and MVPA), and health-related variables (history of chronic diseases and HT use). All models for accelerometer-measured sedentary time were also adjusted for wear time. Models for accelerometer-measured sedentary time adjusted for accelerometer-measured MPVA, and those for self-reported sedentary time adjusted for self-reported MVPA.

Multicollinearity between variables was evaluated using tolerance values, with a value <0.10 indicating multicollinearity. However, multicollinearity was not observed in

any of the models. Tests for linear trend were performed by including sedentary time variables as continuous variables in the models. Interactions between sedentary time and race/ethnicity, SPPB physical performance score, and MVPA were tested by including product terms of these factors with sedentary time in the models. Results were stratified by the median of MVPA based on an a priori assumption that associations of sedentary time with LTL may vary by level of MVPA.[18-21] Cutpoints of 0.5 hours/day of MVPA, based on current recommendations of ≥30 minutes/day of MVPA for adults[43], and 0.36 hours/day (which equates to 2.5 hours/week based on current guidelines), were also used. *P*-values were two-tailed and considered nominally statistically significant at $p<0.05$. All analyses were performed using SAS Version 9.3 (SAS Institute Inc., Cary, NC).

**Results**

In the overall sample, there were 863 (58.3%) white and 618 (41.7%) African American women. Women were on average aged 79.2 (standard deviation [SD] 6.7) years old, ranging from 64 to 95 years old. Women wore the accelerometer for an average of 14.7 (SD 1.3) hours/day over an average of 6.3 (SD 0.8) days. The mean (standard error [SE]) of accelerometer-measured sedentary time was 9.2 (0.04) hours/day, and the mean (SD) of self-reported sedentary time was 8.6 (4.3) hours/day. The mean (SE) of accelerometer-measured MVPA was 0.8 (0.01) hours/day, and the mean (SD) of self-reported MVPA was 0.5 (0.6) hours/day. Accelerometer-measured and self-reported sedentary time were weakly correlated ($r=0.27$; $p<0.001$); accelerometer-measured and self-reported MVPA were similarly weakly correlated ($r=0.28$; $p<0.001$). Mean LTL was 6.6 (SD 0.6) kb and ranged from 4.9 to 8.9 kb. LTL was inversely associated with age

(r=-0.38; p<0.001) and longer in African-American than white women (age-adjusted mean [SE]=6.75 [0.02] and 6.52 [0.02], respectively; $p$<0.001).

Women with greater amounts of accelerometer-measured sedentary time were more likely to be older, white, and obese (Table 4.1). They were also more likely to have high blood pressure, a history of chronic diseases, lower physical performance score, fewer hours/day of MVPA, and to have experienced a fall in the past 12 months. Women with higher self-reported sedentary time were more likely to be older, white, and obese, and have a history of chronic diseases (Table 4.2). They also had lower physical performance score and lower levels of self-reported MVPA, and were less likely to be in excellent or very good health.

In a model adjusted only for wear time, accelerometer-measured sedentary time was significantly associated with LTL (Table 4.3; $p_{trend}$=<0.001). After further adjustment for age and race/ethnicity, findings were no longer significant; in additional models, no significant findings were observed. After stratifying by the median of accelerometer-measured MVPA (0.69 hours/day), significant associations between sedentary time and LTL were not observed among those with MVPA levels above the median (Table 4.4; $p_{interaction}$=0.80). Among women at or below the median MVPA level, sedentary time was inversely associated with LTL after adjusting for wear time, age, race/ethnicity, education, marital status, smoking, alcohol consumption, and BMI ($p_{trend}$=0.02). On average, LTL was 160 (95% confidence interval [CI] 10-320) and 190 (95% CI 30-350) base pairs shorter in women with 9.24-<10.22 or ≥10.22 compared with <8.18 hours of sedentary time/day, respectively. After additional adjustment for a history of chronic diseases and HT use, only women in the highest quartile of sedentary time had

significantly shorter LTL than those who were least sedentary, with an average difference of 170 (95% CI 4-340) base pairs.

After stratification by a cutpoint of 0.5 hours/day of MVPA, *p*-values for trend remained significant in women with <0.5 hours/day of MVPA. At a cutpoint of 0.36 hours/day of MVPA, associations of accelerometer-measured sedentary time with LTL were stronger among those with <0.36 hours/day of MVPA; LTL was 369 (95% CI 60-679) base pairs shorter among the most compared with the least sedentary women in the fully adjusted model. Sedentary time was not significantly associated with LTL in women with ≥0.36 or ≥0.5 hours/day of MVPA (data not shown).

In the unadjusted model, self-reported sedentary time was significantly associated with LTL (Table 4.5; $p_{trend}$=<0.01). In subsequent models adjusting for age, race/ethnicity, and other factors, findings were no longer significant. Results did not vary by level of self-reported MVPA (data not shown).

Results did not vary by race/ethnicity, physical performance score, or after exclusion of participants with a history of cancer (data not shown).

**Discussion**

Among older women who were less physically active as measured by accelerometry, a greater amount of accelerometer-measured sedentary time was significantly associated with shorter LTL. Findings persisted after adjustment for demographic characteristics, lifestyle behaviors, and BMI, but were attenuated after adjustment for a history of chronic diseases and HT use. These findings have important

implications to an aging population, in which greater time spent sedentary and less physical activity tends to be the norm.[23]

We observed that self-reported sedentary time was not associated with LTL, similar to a study in 7,813 Nurses' Health Study participants aged on average 59 years old.[12] Although results were not stratified by physical activity in the Nurses' Health Study, joint classification of sedentary time and physical activity through a combined variable showed that women who were less active and more sedentary had shorter LTL than those who were more active and less sedentary. A study among 2,401 primarily female white twins aged on average 49 years old observed that LTL of inactive participants was 200 base pairs shorter than the most active participants[8]; however, total sedentary time was not specifically evaluated. It is difficult to directly compare our results with those of other studies due to differences in sample size, methods used to assess sedentary time, age ranges of the study populations, and low correlation between accelerometer-measured and self-reported sedentary time. Unlike previous studies, our study focused on older women and used accelerometer-measured sedentary time, an important consideration given that time spent sedentary may be underestimated in self-reported data.[15] An absence of association between self-reported sedentary time and LTL may, to a large extent, reflect measurement imprecision of questionnaire assessments of sedentary time, particularly in older adults.

In previous investigations examining joint effects of sedentary time and physical activity on adverse health outcomes, disease and mortality risks associated with higher sedentary time were either attenuated or eliminated among those engaging in greater amounts of physical activity, and were stronger in those with lower levels of physical

activity.[18-21] These data support a potential biologic interaction between sedentary time and MVPA. In our study, accelerometer-measured sedentary time was not associated with LTL among women who were more physically active. Additionally, sedentary time was not associated with LTL in women meeting current public health recommendations of ≥30 minutes/day of MVPA[43]; in those not meeting this recommendation, higher sedentary time was associated with shorter LTL. Our findings suggest that prolonged sedentary time may be associated with shorter LTL when adequate levels of MVPA are not attained. Conversely, attaining adequate levels of MVPA may act as a buffer against any potentially harmful effect of sedentary time on LTL.

We observed that women spent an average of 9.2 hours/day sedentary according to accelerometer, in concordance with other studies among older adults.[44-46] A study among 7,247 older Women's Health Study participants also observed an average of 9.2 hours/day spent in accelerometer-measured sedentary time.[44] In our study, women reported spending an average of 8.6 hours/day sedentary. This is much higher than total self-reported sedentary time observed in previous studies among older adults, which has ranged from 5.2-6.7 hours/day.[23] We also observed that African American women spent less time sedentary than white women. A previous study in a national sample of adults observed that white and African American women have similar patterns of sedentary behavior[47]; however, older adults were not specifically evaluated.

Several mechanisms may explain the association of sedentary time with LTL. Oxidative stress and inflammation accelerate telomere attrition.[2,11,48] It has been shown that regular engagement in physical activity increases anti-oxidant activity and may induce anti-inflammatory responses.[49,50] Therefore, it is possible that women who spend

long hours sedentary coupled with less time in MVPA may not be exposed to these anti-oxidant and anti-inflammatory defenses. Increased time spent sedentary and inactivity may lead to insulin resistance[51], which has been previously associated with short LTL.[52] The association of sedentary time with LTL may also be due to mediation by obesity. In previous studies, engaging in higher amounts of sedentary behavior was associated with an increased risk of obesity[25], and obesity has been associated with shorter LTL[7]; however, findings persisted after adjustment for BMI. Reverse causation due to chronic disease burden may also be possible; that is, women who have a history of chronic diseases may be more likely to have a sedentary lifestyle and shorter LTL.

Limitations of our study included the cross-sectional design, which precluded our ability to assess a temporal relation between sedentary time and LTL. Our study was exclusive to older women, and our findings cannot be generalized to men or younger women. Our results apply to telomere length dynamics in leukocytes but not in other tissues. Women who enrolled in the WHI ES and LLS were more likely to be healthier at baseline, thus those who experienced greater health-related LTL shortening may have been excluded. Strengths included the diverse sample, adjustment for a large number of potential confounders, adjudicated data for chronic diseases, and accelerometer-measured sedentary time and MVPA.

In summary, higher accelerometer-measured sedentary time was associated with shorter LTL among less physically active women. However, in more physically active women, there was no association of accelerometer-measured sedentary time with LTL. Collectively, our findings suggest that prolonged sedentary time and limited engagement in MVPA may act synergistically to shorten LTL among older adults. Therefore,

avoidance of a highly inactive lifestyle may provide health benefits at the cellular level. Longitudinal studies assessing sedentary time and MVPA in relation to changes in LTL are currently needed.

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Table 4.1: Characteristics of Older Women in the Women's Health Initiative Objective Physical Activity and Cardiovascular Health Study by Accelerometer-Measured Sedentary Time

| Characteristic | Accelerometer-measured sedentary time (h/day) | | | | *P*-value |
|---|---|---|---|---|---|
| | <8.18 (n=322) | 8.18-<9.24 (n=326) | 9.24-<10.22 (n=324) | ≥10.22 (n=325) | |
| Age (years), mean (SD) | 77.8 (6.6) | 78.9 (6.8) | 79.6 (6.7) | 80.4 (6.5) | <0.001 |
| Age (years), No. (%) | (n=322) | (n=326) | (n=324) | (n=325) | |
| 64-69 | 36 (11.2) | 32 (9.8) | 26 (8.0) | 19 (5.9) | |
| 70-74 | 71 (22.1) | 66 (20.3) | 62 (19.1) | 46 (14.2) | |
| 75-79 | 83 (25.8) | 67 (20.6) | 56 (17.3) | 61 (18.8) | <0.001 |
| 80-84 | 84 (26.1) | 78 (23.9) | 93 (28.7) | 110 (33.9) | |
| ≥85 | 48 (14.9) | 83 (25.5) | 87 (26.9) | 89 (27.4) | |
| Race/ethnicity, No. (%) | (n=322) | (n=326) | (n=324) | (n=325) | |
| White | 155 (48.1) | 181 (55.5) | 196 (60.5) | 224 (68.9) | <0.001 |
| African American | 167 (51.9) | 145 (44.5) | 128 (39.5) | 101 (31.1) | |
| Education[a], No. (%) | (n=322) | (n=324) | (n=322) | (n=324) | |
| Less than high school | 14 (4.4) | 9 (2.8) | 9 (2.8) | 12 (3.7) | |
| High school | 50 (15.5) | 50 (15.4) | 53 (16.5) | 50 (15.4) | 0.79 |
| Some college | 107 (33.2) | 126 (38.9) | 124 (38.5) | 129 (39.8) | |
| College graduate | 151 (46.9) | 139 (42.9) | 136 (42.2) | 133 (41.1) | |
| Baseline marital status[a], No. (%) | (n=321) | (n=324) | (n=324) | (n=324) | |
| Married/living as married | 190 (59.2) | 194 (59.9) | 183 (56.5) | 177 (54.6) | |
| Widowed | 46 (14.3) | 55 (17.0) | 56 (17.3) | 68 (21.0) | 0.48 |
| Divorced/separated | 73 (22.7) | 60 (18.5) | 75 (23.2) | 65 (20.1) | |
| Never married | 12 (3.7) | 15 (4.6) | 10 (3.1) | 14 (4.3) | |
| Baseline smoking history[a], No. (%) | (n=320) | (n=325) | (n=318) | (n=320) | |
| Never smoked | 170 (53.1) | 183 (56.3) | 172 (54.1) | 169 (52.8) | |
| Past smoker | 133 (41.6) | 127 (39.1) | 115 (36.2) | 133 (41.6) | 0.12 |
| Current smoker | 17 (5.3) | 15 (4.6) | 31 (9.8) | 18 (5.6) | |
| Baseline alcohol consumption[a], No. (%) | (n=318) | (n=325) | (n=323) | (n=325) | |
| Non-drinker | 40 (12.6) | 37 (11.4) | 35 (10.8) | 40 (12.3) | |
| Past drinker | 61 (19.2) | 68 (20.9) | 71 (22.0) | 56 (17.2) | 0.81 |
| Current drinker | 217 (68.2) | 220 (67.7) | 217 (67.2) | 229 (70.5) | |

All characteristics represent current status, unless otherwise noted

[a]Determined at the 1993-1998 baseline visit

[b]Adjusted for hours of wear time

BMI, body mass index; CHD, coronary heart disease; H, hours; EPESE, Established Populations for Epidemiologic Studies of the Elderly; LTL, leukocyte telomere length; SD, standard deviation; SE, standard error

Table 4.1: Characteristics of Older Women in the Women's Health Initiative Objective Physical Activity and Cardiovascular Health Study by Accelerometer-Measured Sedentary Time, Continued

| Characteristic | Accelerometer-measured sedentary time (h/day) | | | | *P*-value |
|---|---|---|---|---|---|
| | <8.18 (n=322) | 8.18-<9.24 (n=326) | 9.24-<10.22 (n=324) | ≥10.22 (n=325) | |
| BMI (kg/m$^2$), No. (%) | (n=321) | (n=321) | (n=322) | (n=319) | |
| Underweight | 6 (1.9) | 3 (0.9) | 4 (1.2) | 3 (0.9) | |
| Normal weight | 125 (38.9) | 106 (33.0) | 96 (29.8) | 65 (20.4) | <0.001 |
| Overweight | 113 (35.2) | 114 (35.5) | 105 (32.6) | 122 (38.2) | |
| Obese | 77 (24.0) | 98 (30.5) | 117 (36.3) | 129 (40.4) | |
| Self-rated health, No. (%) | (n=310) | (n=316) | (n=305) | (n=312) | |
| Excellent | 42 (13.6) | 22 (7.0) | 25 (8.2) | 25 (8.0) | |
| Very good | 131 (42.3) | 143 (45.3) | 126 (41.3) | 119 (38.1) | 0.07 |
| Good | 112 (36.1) | 120 (38.0) | 116 (38.0) | 134 (43.0) | |
| Fair/poor | 25 (8.1) | 31 (9.8) | 38 (12.5) | 34 (10.9) | |
| Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, No. (%) | (n=315) 52 (16.5) | (n=323) 44 (13.6) | (n=321) 68 (21.2) | (n=318) 68 (21.4) | 0.03 |
| History of hypertension, No. (%) | (n=322) 252 (78.3) | (n=326) 263 (80.7) | (n=324) 268 (82.7) | (n=325) 261 (80.3) | 0.56 |
| History of hormone therapy use, No. (%) | (n=315) 224 (71.1) | (n=320) 210 (65.6) | (n=321) 228 (71.0) | (n=320) 231 (72.2) | 0.26 |
| History of chronic diseases, No. (%) | (n=322) | (n=326) | (n=324) | (n=325) | |
| CHD | 14 (4.4) | 16 (4.9) | 19 (5.9) | 30 (9.2) | 0.04 |
| Stroke | 10 (3.1) | 4 (1.2) | 16 (4.9) | 11 (3.4) | 0.06 |
| Diabetes | 49 (15.2) | 71 (21.8) | 71 (21.9) | 76 (23.4) | 0.05 |
| Cancer | 43 (13.4) | 67 (20.6) | 68 (21.0) | 63 (19.4) | 0.05 |
| Any disease | 104 (32.3) | 135 (41.4) | 141 (43.5) | 140 (43.1) | 0.01 |
| Experienced a fall in the past 12 months, No. (%) | (n=310) 74 (23.9) | (n=310) 106 (34.2) | (n=316) 102 (32.3) | (n=316) 99 (31.3) | 0.03 |
| EPESE short physical performance score, mean (SD) | 8.5 (2.2) | 8.2 (2.4) | 7.9 (2.7) | 7.4 (2.6) | <0.001 |

All characteristics represent current status, unless otherwise noted

[a]Determined at the 1993-1998 baseline visit

[b]Adjusted for hours of wear time

BMI, body mass index; CHD, coronary heart disease; H, hours; EPESE, Established Populations for Epidemiologic Studies of the Elderly; LTL, leukocyte telomere length; SD, standard deviation; SE, standard error

Table 4.1: Characteristics of Older Women in the Women's Health Initiative Objective Physical Activity and Cardiovascular Health Study by Accelerometer-Measured Sedentary Time, Continued

| Characteristic | Accelerometer-measured sedentary time (h/day) | | | | *P*-value |
|---|---|---|---|---|---|
| | <8.18 (n=322) | 8.18-<9.24 (n=326) | 9.24-<10.22 (n=324) | ≥10.22 (n=325) | |
| Accelerometer-measured hours of moderate-to-vigorous physical activity/day, mean (SE)[b] | 1.24 (0.02) | 0.86 (0.02) | 0.68 (0.02) | 0.39 (0.02) | <0.001 |
| Self-reported hours of sedentary time/day, mean (SD) | 7.2 (3.6) | 8.3 (4.1) | 9.2 (4.4) | 10.0 (4.2) | <0.001 |
| LTL (kilobases), mean (SD) | 6.70 (0.59) | 6.68 (0.60) | 6.56 (0.60) | 6.54 (0.60) | <0.001 |
| Age and race-adjusted LTL (kilobases), mean (SE) | 6.66 (0.03) | 6.68 (0.03) | 6.60 (0.03) | 6.62 (0.03) | 0.20 |

All characteristics represent current status, unless otherwise noted

[a]Determined at the 1993-1998 baseline visit

[b]Adjusted for hours of wear time

BMI, body mass index; CHD, coronary heart disease; H, hours; EPESE, Established Populations for Epidemiologic Studies of the Elderly; LTL, leukocyte telomere length; SD, standard deviation; SE, standard error

Table 4.2: Characteristics of Older Women in the Women's Health Initiative Objective Physical Activity and Cardiovascular Health Study by Self-Reported Sedentary Time

| Characteristic | Self-reported sedentary time (h/day) | | | | *P*-value |
|---|---|---|---|---|---|
| | <6 (n=329) | 6 -<8 (n=279) | 8-<11 (n=382) | ≥11 (n=393) | |
| Age (years), mean (SD) | 77.7 (6.1) | 79.3 (6.6) | 79.7 (6.7) | 79.4 (7.1) | <0.001 |
| Age (years), No. (%) | (n=329) | (n=279) | (n=382) | (n=393) | |
| 64-69 | 39 (11.9) | 19 (6.8) | 31 (8.1) | 37 (9.4) | |
| 70-74 | 69 (21.0) | 51 (18.3) | 66 (17.3) | 78 (19.9) | |
| 75-79 | 78 (23.7) | 71 (25.5) | 72 (18.9) | 58 (14.8) | <0.001 |
| 80-84 | 101 (30.7) | 74 (26.5) | 110 (28.8) | 115 (29.3) | |
| ≥85 | 42 (12.8) | 64 (22.9) | 103 (27.0) | 105 (26.7) | |
| Race/ethnicity, No. (%) | (n=329) | (n=279) | (n=382) | (n=393) | |
| White | 144 (43.8) | 160 (57.4) | 243 (63.6) | 257 (65.4) | <0.001 |
| African American | 185 (56.2) | 119 (42.7) | 139 (36.4) | 136 (34.6) | |
| Education[a], No. (%) | (n=328) | (n=279) | (n=381) | (n=390) | |
| Less than high school | 9 (2.7) | 11 (3.9) | 14 (3.7) | 9 (2.3) | |
| High school | 57 (17.4) | 38 (13.6) | 59 (15.5) | 58 (14.9) | 0.70 |
| Some college | 129 (39.3) | 98 (35.1) | 137 (36.0) | 153 (39.2) | |
| College graduate | 133 (40.6) | 132 (47.3) | 171 (44.9) | 170 (43.6) | |
| Baseline marital status[a], No. (%) | | | | | |
| Married/living as | (n=329) | (n=276) | (n=381) | (n=391) | |
| married | 187 (56.8) | 148 (53.6) | 230 (60.4) | 214 (54.7) | |
| Widowed | 60 (18.2) | 50 (18.1) | 66 (17.3) | 67 (17.1) | 0.67 |
| Divorced/separated | 71 (21.6) | 67 (24.3) | 71 (18.6) | 89 (22.8) | |
| Never married | 11 (3.3) | 11 (4.0) | 14 (3.7) | 21 (5.4) | |
| Baseline smoking history[a], No. (%) | (n=322) | (n=278) | (n=379) | (n=390) | |
| Never smoked | 179 (55.6) | 150 (54.0) | 210 (55.4) | 203 (52.1) | |
| Past smoker | 122 (37.9) | 113 (40.7) | 149 (39.3) | 156 (40.0) | 0.74 |
| Current smoker | 21 (6.5) | 15 (5.4) | 20 (5.3) | 31 (8.0) | |
| Baseline alcohol consumption[a], No. (%) | (n=327) | (n=276) | (n=382) | (n=392) | |
| Non-drinker | 47 (14.4) | 35 (12.7) | 41 (10.7) | 41 (10.5) | |
| Past drinker | 78 (23.9) | 44 (15.9) | 66 (17.3) | 79 (20.2) | 0.06 |
| Current drinker | 202 (61.8) | 197 (71.4) | 275 (72.0) | 272 (69.4) | |

All characteristics represent current status, unless otherwise noted

[a]Determined at the 1993-1998 baseline visit

[b]Adjusted for hours of wear time

BMI, body mass index; CHD, coronary heart disease; EPESE, Established Populations for Epidemiologic Studies of the Elderly; H, hours; LTL, leukocyte telomere length; SD, standard deviation; SE, standard error

Table 4.2: Characteristics of Older Women in the Women's Health Initiative Objective Physical Activity and Cardiovascular Health Study by Self-Reported Sedentary Time, Continued

| Characteristic | Self-reported sedentary time (h/day) | | | | *P*-value |
|---|---|---|---|---|---|
| | <6 (n=329) | 6 -<8 (n=279) | 8-<11 (n=382) | ≥11 (n=393) | |
| BMI (kg/m$^2$), No. (%) | (n=325) | (n=278) | (n=378) | (n=387) | |
| Underweight | 4 (1.2) | 3 (1.1) | 5 (1.3) | 4 (1.0) | |
| Normal weight | 106 (32.6) | 98 (35.3) | 120 (31.8) | 95 (24.6) | <0.001 |
| Overweight | 111 (34.2) | 106 (38.1) | 141 (37.3) | 118 (30.5) | |
| Obese | 104 (32.0) | 71 (25.5) | 112 (29.6) | 170 (43.9) | |
| Self-rated health, No. (%) | (n=311) | (n=274) | (n=368) | (n=372) | |
| Excellent | 38 (12.2) | 24 (8.8) | 33 (9.0) | 30 (8.1) | |
| Very good | 127 (40.8) | 133 (48.5) | 156 (42.4) | 120 (32.3) | <0.001 |
| Good | 121 (38.9) | 100 (36.5) | 145 (39.4) | 163 (43.8) | |
| Fair/poor | 25 (8.0) | 17 (6.2) | 34 (9.2) | 59 (15.9) | |
| Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, No. (%) | (n=323) 54 (16.7) | (n=271) 48 (17.7) | (n=381) 62 (16.3) | (n=380) 74 (19.5) | 0.67 |
| History of hypertension, No. (%) | (n=329) 262 (79.6) | (n=279) 211 (75.6) | (n=382) 309 (80.9) | (n=393) 329 (83.7) | 0.07 |
| History of hormone therapy use, No. (%) | (n=323) 214 (66.3) | (n=273) 190 (69.6) | (n=377) 271 (71.9) | (n=390) 283 (72.6) | 0.26 |
| History of chronic diseases, No. (%) | (n=329) | (n=279) | (n=382) | (n=393) | |
| CHD | 15 (4.6) | 19 (6.8) | 22 (5.8) | 27 (6.9) | 0.55 |
| Stroke | 16 (4.9) | 10 (3.6) | 13 (3.4) | 12 (3.1) | 0.61 |
| Diabetes | 60 (18.2) | 64 (22.9) | 71 (18.6) | 107 (27.2) | <0.01 |
| Cancer | 46 (14.0) | 56 (20.1) | 78 (20.4) | 71 (18.1) | 0.12 |
| Any disease | 111 (33.7) | 122 (43.7) | 152 (40.0) | 180 (45.8) | <0.01 |
| Experienced a fall in the past 12 months, No. (%) | (n=322) 88 (27.3) | (n=275) 83 (30.2) | (n=375) 117 (31.2) | (n=387) 136 (35.1) | 0.16 |
| EPESE short physical performance score, mean (SD) | 8.3 (2.5) | 8.4 (2.3) | 8.0 (2.5) | 7.5 (2.7) | <0.001 |

All characteristics represent current status, unless otherwise noted

[a]Determined at the 1993-1998 baseline visit

[b]Adjusted for hours of wear time

BMI, body mass index; CHD, coronary heart disease; EPESE, Established Populations for Epidemiologic Studies of the Elderly; H, hours; LTL, leukocyte telomere length; SD, standard deviation; SE, standard error

Table 4.2: Characteristics of Older Women in the Women's Health Initiative Objective Physical Activity and Cardiovascular Health Study by Self-Reported Sedentary Time, Continued

| Characteristic | Self-reported sedentary time (h/day) | | | | *P*-value |
|---|---|---|---|---|---|
| | <6 (n=329) | 6 -<8 (n=279) | 8-<11 (n=382) | ≥11 (n=393) | |
| Accelerometer-measured hours of sedentary time/day, mean (SE)[c] | 8.63 (0.08) | 8.96 (0.09) | 9.32 (0.07) | 9.66 (0.07) | <0.001 |
| Self-reported hours of moderate-to-vigorous physical activity/day mean (SD) | 0.7 (0.8) | 0.5 (0.5) | 0.5 (0.6) | 0.4 (0.5) | <0.001 |
| LTL (kilobases) at 2012-2013, mean (SD) | 6.71 (0.61) | 6.63 (0.56) | 6.58 (0.58) | 6.61 (0.63) | 0.04 |
| Age and race-adjusted LTL (kilobases) at 2012-2013, mean (SE) | 6.66 (0.03) | 6.66 (0.03) | 6.63 (0.03) | 6.65 (0.03) | 0.86 |

All characteristics represent current status, unless otherwise noted

[a]Determined at the 1993-1998 baseline visit

[b]Adjusted for hours of wear time

BMI, body mass index; CHD, coronary heart disease; EPESE, Established Populations for Epidemiologic Studies of the Elderly; H, hours; LTL, leukocyte telomere length; SD, standard deviation; SE, standard error

Table 4.3: Association of Accelerometer-Measured Sedentary Time with Leukocyte Telomere Length (in Kilobases) among Older Women

| | Accelerometer-measured sedentary time, hours/day | | | | |
|---|---|---|---|---|---|
| | <8.18 β (95% CI) | 8.18-<9.24 β (95% CI) | 9.24-<10.22 β (95% CI) | ≥10.22 β (95% CI) | *P*-value for trend |
| Model 1[a] | Ref | -0.04 (-0.13,0.05) | -0.17 (-0.26, -0.07) | -0.21 (-0.31, -0.12) | <0.001 |
| Model 2[b] | Ref | 0.01 (-0.07,0.10) | -0.08 ( -0.16,0.01) | -0.07 ( -0.16,0.01) | 0.05 |
| Model 3[c] | Ref | 0.01 (-0.07,0.10) | -0.07 ( -0.16,0.02) | -0.06 ( -0.16,0.03) | 0.11 |
| Model 4[d] | Ref | 0.02 (-0.06,0.11) | -0.06 ( -0.15,0.03) | -0.06 ( -0.16,0.04) | 0.15 |
| Model 5[e] | Ref | 0.02 (-0.07,0.11) | -0.07 ( -0.17,0.03) | -0.07 ( -0.18,0.04) | 0.17 |
| Model 6[f] | Ref | 0.03 (-0.06,0.12) | -0.06 ( -0.16,0.04) | -0.06 ( -0.18,0.05) | 0.22 |

[a]Model 1: Adjusted for wear hours (n=1297)
[b]Model 2: Adjusted for model 1 + age and race/ethnicity (n=1297)
[c]Model 3: Adjusted for model 2 + education and baseline marital status, smoking, and alcohol consumption (n=1270)
[d]Model 4: Adjusted for model 3 + body mass index (n=1256)
[e]Model 5: Adjusted for model 4 + hours/day of moderate-to-vigorous intensity physical activity (n=1256)
[f]Model 6: Adjusted for model 5 + history of chronic diseases and hormone therapy use (n=1235)

Table 4.4: Association of Accelerometer-Measured Sedentary Time with Leukocyte Telomere Length (in Kilobases) by Hours/Day of Accelerometer-Measured Moderate-to-Vigorous Intensity Physical Activity among Older Women

| | Accelerometer-measured sedentary time, hours/day | | | | |
|---|---|---|---|---|---|
| | <8.18 β (95% CI) | 8.18-<9.24 β (95% CI) | 9.24-<10.22 β (95% CI) | ≥10.22 β (95% CI) | *P*-value for trend |
| ≤0.69 hours/day of MVPA | | | | | |
| Model 1[a] | Ref | -0.03 (-0.19,0.13) | -0.16 (-0.32, -0.002) | -0.21 (-0.38, -0.05) | <0.01 |
| Model 2[b] | Ref | -0.03 (-0.18,0.12) | -0.14 ( -0.29,0.01) | -0.16 (-0.31, -0.002) | 0.03 |
| Model 3[c] | Ref | -0.06 (-0.21,0.09) | -0.17 (-0.32, -0.02) | -0.19 (-0.35, -0.03) | 0.02 |
| Model 4[d] | Ref | -0.05 (-0.21,0.10) | -0.16 (-0.32, -0.01) | -0.19 (-0.35, -0.03) | 0.02 |
| Model 5[e] | Ref | -0.04 (-0.20,0.11) | -0.15 ( -0.31,0.01) | -0.17 (-0.34, -0.004) | 0.25 |
| >0.69 hours/day of MVPA | | | | | |
| Model 1[a] | Ref | -0.01 (-0.13,0.11) | -0.11 ( -0.24,0.02) | -0.11 ( -0.27,0.05) | 0.07 |
| Model 2[b] | Ref | 0.04 (-0.07,0.14) | -0.05 ( -0.17,0.07) | -0.02 ( -0.17,0.13) | 0.45 |
| Model 3[c] | Ref | 0.04 (-0.07,0.15) | -0.03 ( -0.15,0.09) | -0.01 ( -0.16,0.14) | 0.68 |
| Model 4[d] | Ref | 0.05 (-0.06,0.16) | -0.02 ( -0.15,0.10) | -0.01 ( -0.16,0.15) | 0.78 |
| Model 5[e] | Ref | 0.07 (-0.05,0.18) | -0.02 ( -0.14,0.11) | -0.02 ( -0.17,0.14) | 0.91 |

[a]Model 1: Adjusted for wear hours (n=653 for ≤0.69 hours/day; n=644 for >0.69 hours/day)
[b]Model 2: Adjusted for model 1 + age and race/ethnicity (n=653 for ≤0.69 hours/day; n=644 for >0.69 hours/day)
[c]Model 3: Adjusted for model 2 + education and baseline marital status, smoking, and alcohol consumption (n=636 for ≤0.69 hours/day; n=634 for >0.69 hours/day)
[d]Model 4: Adjusted for model 3 + body mass index (n=629 for ≤0.69 hours/day; n=627 for >0.69 hours/day)
[e]Model 5: Adjusted for model 4 + history of chronic diseases and hormone therapy use (n=620 for ≤0.69 hours/day; n=615 for >0.69 hours/day)

Table 4.5: Association of Self-Reported Sedentary Time with Leukocyte Telomere Length (in Kilobases) among Older Women

| | Self-reported sedentary time, hours/day | | | | |
|---|---|---|---|---|---|
| | <6<br>β (95% CI) | 6-<8<br>β (95% CI) | 8-<11<br>β (95% CI) | ≥11<br>β (95% CI) | *P*-value for trend |
| Model 1[a] | Ref | -0.07 (-0.17,0.02) | -0.13 (-0.22, -0.04) | -0.10 (-0.19, -0.01) | <0.01 |
| Model 2[b] | Ref | 0.0002 (-0.09,0.09) | -0.03 ( -0.11,0.05) | -0.01 (-0.09, 0.08) | 0.43 |
| Model 3[c] | Ref | 0.01 (-0.08,0.10) | -0.01 ( -0.10,0.07) | 0.01 ( -0.07,0.10) | 0.73 |
| Model 4[d] | Ref | 0.01 (-0.08,0.10) | -0.01 ( -0.09,0.07) | 0.02 ( -0.07,0.10) | 0.86 |
| Model 5[e] | Ref | 0.02 (-0.07,0.11) | 0.0001 ( -0.08,0.08) | 0.03 (-0.06, 0.11) | 0.96 |
| Model 6[f] | Ref | 0.03 (-0.06,0.12) | 0.001 ( -0.08,0.09) | 0.04 ( -0.05,0.12) | 0.81 |

[a]Model 1: Unadjusted (n=1383)
[b]Model 2: Adjusted for model 1 + age and race/ethnicity (n=1383)
[c]Model 3: Adjusted for model 2 + education and baseline marital status, smoking, and alcohol consumption (n=1354)
[d]Model 4: Adjusted for model 3 + body mass index (n=1339)
[e]Model 5: Adjusted for model 4 + hours/day of moderate-to-vigorous intensity physical activity (n=1339)
[f]Model 6: Adjusted for model 5 + history of chronic diseases and hormone therapy use (n=1319)

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# CHAPTER 5: DISCUSSION AND CONCLUSIONS

Achieving longevity and reaching old age with intact health and function are overarching public health goals. The US aging population is rapidly growing.[1] Currently, there are 1.3 million women aged 90 or above in the United States; by 2050, it is expected that over 4 million women will be in this age group.[2] Therefore, research on factors predicting longevity and extending healthy years of life is becoming increasingly important.

This dissertation had three objectives: 1) Evaluate the associations of ages at menarche and menopause and reproductive lifespan with exceptional longevity in postmenopausal women; 2) Determine whether genetic variants associated with longevity in previous studies among populations of European descent were associated with survival to ages 85 and 90 and healthy aging in postmenopausal white, African-American, and Hispanic women; and 3) Assess associations of accelerometer-measured and self-reported sedentary time with LTL, a purported biomarker of cellular aging, among older women.

In Chapter 2, I observed that of 16,251 women, 8,892 (55%) survived to age 90. The odds of survival to age 90 were modestly elevated in women aged ≥12 years at menarche (OR, 1.09; 95% CI, 1.00-1.19). Furthermore, women with later age at menopause were more likely to achieve exceptional longevity than those with early menopause ($P_{trend}$=0.01). Women who were aged ≥55 years old at menopause had an 18% (OR, 1.18; 95% CI, 1.02-1.36) increased odds of exceptional longevity compared with those who had menopause at <40 years. Women with >40 reproductive years were 13% (OR, 1.13; 95% CI, 1.03-1.25) more likely to survive to age 90 than those with <33 reproductive years.

In Chapter 3, I observed that among white women, three SNPs located at or near the *APOE* gene (rs2075650, rs4420638, and rs429358) were significantly associated with survival to age 90. Furthermore, rs4420638 and rs429358 were significantly associated with healthy aging, defined as survival to age 85 free of major age-related diseases and without physical impairment or assistance in ADL. Among African-American women, no SNPs were significantly associated with the aging phenotypes. Among Hispanic women, SNPs in LD with a SNP previously associated with longevity in a GWAS among European-Americans (rs2149954) were significantly associated with survival to age 85.

In Chapter 4, I found that self-reported and accelerometer-measured sedentary time overall were not associated with LTL. However, in stratified analyses among women who were less physically active, accelerometer-measured sedentary time was inversely associated with LTL. Those in the highest quartile of sedentary time had significantly shorter telomeres than those in the lowest quartile. The negative relationship between accelerometer-measured sedentary time and LTL was even stronger among women who did not meet recommendations of ≥2.5 hours/week of MVPA among older adults (based on <0.36 hours/day of MPVA). However, accelerometer-measured sedentary time was not associated with LTL among women meeting current recommendations. These stratum-specific differences were not statistically significant when tested with a multiplicative interaction term. However, the literature on sedentary time and mortality is strongly supportive of a similar pattern of association. Therefore, a biologic interaction is possible, even in the absence of a statistical interaction.[3]

Findings from this dissertation reveal important insights into reproductive, genetic, and lifestyle factors that may affect chronological and cellular aging among

postmenopausal women. Women who experience menarche and menopause at a later age may be more likely to experience a longer lifespan. Furthermore, genetic factors, such as *APOE*, may influence a woman's likelihood of living a long and healthy life. Total sedentary time combined with low physical activity may be associated with shorter LTL, a postulated biomarker of aging. These findings suggest that a woman's lifespan and healthspan may be determined by a host of heritable and dynamic components.

The mechanistic underpinnings of aging are still under investigation.[1,4] It is highly likely that aging is influenced by a complex interplay of multiple biochemical, genetic, physiological, behavioral, psychological, economic, and societal factors.[1,4,5] However, no study to date has evaluated the interconnectedness between these factors in the setting of chronological and cellular aging.

From an epidemiological perspective, factors that may be associated with chronological aging include demographic characteristics (e.g., race/ethnicity and educational attainment), cardiovascular risk factors (e.g., blood pressure, cholesterol, and glucose intolerance), lifestyle behaviors (e.g., smoking, diet, and physical activity), and genetic factors.[1] Environmental and genetic factors may in turn interact to achieve longevity. Genetic and lifestyle factors may also be determinants of cellular aging.[4,5] A recent review highlighted the nine hallmarks of cellular aging, such as genomic instability, telomere attrition, and epigenetic alterations, and concluded that all hallmarks are interconnected.[4] For example, aging-related changes in one tissue can influence aging of other tissues, and senescent cells (i.e., cells that cease to divide) can cause neighboring cells to become senescent. Collectively, these observations highlight the intricacies involved in aging phenotypes.

It is indeed possible that reproductive factors, genetic factors, and sedentary time may be interconnected in determining length of life and influencing cellular aging among postmenopausal women. For example, age at menopause and longevity may be due to a similar set of genetic factors.[1] A GWAS of age at natural menopause identified genetic variants involved in DNA replication and repair pathways, which are pathways central to aging.[1,7] Specifically, the DNA repair gene exonuclease 1 (*EXO1*) was significantly associated with age at menopause and has been previously associated with increased life expectancy among female centenarians.[8] Although LTL has also been shown to be due to genetic factors and is largely established at birth[9,10], it is currently unknown whether similar genes and pathways determine age at menopause, longevity, and LTL. However, age at menopause has been shown to be associated with LTL.[11,12] In a study among white women ages 65 and older, later age at menopause was associated with longer LTL.[11] Later age at menopause and longer LTL have both been associated with increased survival and decreased risk of similar age-related diseases such as cardiovascular disease and type 2 diabetes.[13-18] Furthermore, avoidance of a highly inactive lifestyle has been associated with longevity, decreased risk of chronic diseases, and longer LTL.[19-21] Taken together, these observations suggest that aging phenotypes may be determined by a complex network involving multiple factors that may not only influence aging but also each other. Examining the potential connections between my exposures of interest and the various aging phenotypes I studied was beyond the scope of this dissertation. The challenge of future studies will be to determine how these and other factors interweave to predict lifespan, health span, and aging at the cellular level.

This dissertation had several limitations. First, it was exclusive to postmenopausal women, and thus findings cannot be generalized to younger women or men. The study population also consisted largely of white women, lowering statistical power to evaluate associations for other racial/ethnic groups. Participants of the WHI may have been healthier at baseline than the general population of postmenopausal women. Furthermore, women who enrolled for additional follow-up were more likely to be white, educated, and healthier at baseline.

Strengths of this dissertation included adjudicated outcome ascertainment, high retention of study participants, and inclusion of racial/ethnic minorities. The studies presented in this dissertation were all novel and assessed previously unexplored hypotheses on factors and potential mechanisms that may underlie aging among postmenopausal women.

This dissertation serves to advance the study of aging in postmenopausal women, an increasingly aging population. Future studies with large numbers of exceptional survivors are warranted to confirm whether ages at menarche and menopause are predictors of a woman's likelihood of living a long life. Additionally, it is important to determine whether other reproductive factors, such as age at childbirth and parity, are associated with prolonged lifespan. Our findings suggest that genetic factors associated with longevity in women of white race/ethnicity are not necessarily associated with longevity in other races. This underscores the importance of conducting genetic studies of aging in women of diverse racial and ethnic backgrounds to determine pathways contributing to exceptional survival in these populations. The link between accelerometer-measured sedentary time and LTL is novel and merits further study. LTL

is largely established at birth and undergoes rapid attrition during the first 20 years of life.[10] Whether health behaviors such as sedentary time and physical activity affect age-dependent telomere attrition in adulthood is controversial. Accordingly, it will be worthwhile to conduct long-term intervention trials to determine whether decreasing sedentary behavior slows LTL attrition, providing crucial evidence as to whether a highly inactive lifestyle confers negative health consequences at the cellular level. Since genetic factors are strongly associated with LTL, these should also be investigated in combination with other health behaviors to determine the precise factors influencing LTL during the adult life course.

Future studies of aging would benefit from developing an integrative model detailing the intricate networks and connections leading to exceptional survival and slower cellular aging, which would lead to a better understanding of how to extend both lifespan and healthspan. This is already being pursued by the National Institutes of Health through the field of geroscience, whose goal is to understand how aging leads to chronic diseases and develop novel, preventive approaches targeting many diseases simultaneously.[5] At an NIH geroscience summit, seven pillars of aging were identified (metabolism; macromolecular damage; epigenetics; inflammation; adaptation to stress; proteostasis; and stem cells and regeneration), and it was concluded that delaying aging and extending health span among older adults will require an understanding of the interdependence of these pillars in inducing aging and chronic diseases. Undoubtedly, future epidemiologic study into the networks of dynamic and heritable components influencing aging will be important in attaining the universal public health goal of living a long and healthy life.

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