Published in final edited form as:

J Am Geriatr Soc. 2017 January ; 65(1): 98–106. doi:10.1111/jgs.14433.

Kidney Function and Disability-Free Survival in Older Women

Alyson Cavanaugh, MPH¹, Andrea Z. LaCroix, PhD², Donna Kritz-Silverstein, PhD², Eileen Rillamas-Sun, PhD, MPH³, and Dena E. Rifkin, MD⁴

¹San Diego State University/University of California, San Diego, Joint Doctoral Program in Public Health (Epidemiology)

²Division of Epidemiology, Department of Family Medicine and Public Health, University of California, San Diego, CA

³Fred Hutchinson Cancer Research Center, Public Health Sciences, Seattle, WA

⁴Division of Nephrology, Department of Preventative Medicine and Public Health, University of California, San Diego, CA

Abstract

OBJECTIVES—To examine the prospective association of kidney function with survival to age 85 with functional independence versus disability or death before age 85.

DESIGN—Prospective study

SETTING—Women's Health Initiative, conducted at 40 U.S. clinical centers

PARTICIPANTS—7,178 postmenopausal women enrolled between 1993–1998 with baseline biomarker assessments who had the potential to reach age 85 before September 2013.

MEASUREMENTS—Kidney function was measured by estimated glomerular filtration rate (eGFR) calculated from serum creatinine collected at baseline. Outcomes included survival to age 85 with functional independence versus survival with disability or death before age 85. Disability was defined as mobility and/or activities of daily living limitations measured by questionnaire.

RESULTS—eGFR (mL/min/1.73m²) was >90 in 22.7% of women, 60–89 in 66.5%, 45–59 in 8.7% and <45 in 2.0%. Median follow-up time was 15 years. Among 4,953 survivors, 3,155 reported no physical disability at age 85. 2225 participants died before age 85. Compared to women with the poorest kidney function (eGFR <45 mL/min/1.73m²), women with eGFR ≥90 had 2.71 times (95% CI 1.62 – 4.51), women with eGFR 60–89 had 3.04 times (95% CI 1.85 – 5.00), and women with eGFR 45–59 had 2.22 times (95% CI 1.31 – 3.76) higher odds of survival to age

Address for Correspondence: Alyson Cavanaugh, MPH, Department of Family Medicine and Public Health, School of Medicine, University of California, San Diego, 9500 Gilman Drive, 0675, La Jolla CA 92093-0675; Phone: 858-822-0627; alcavana@ucsd.edu.
Address for Reprints: Alyson Cavanaugh, MPH, Department of Family Medicine and Public Health, School of Medicine, University of California, San Diego, 9500 Gilman Drive, 0675, La Jolla CA 92093-0675; Phone: 858-822-0627; alcavana@ucsd.edu

Author Contributions: Alyson Cavanaugh contributed to the design of the statistical analysis and manuscript, performed the data analysis, interpreted data, drafted the manuscript, revised the manuscript, and approved the final version. Andrea Z. LaCroix, Donna Kritz-Silverstein, and Dena Rifkin contributed to the design of the statistical analysis and manuscript, interpreted data, revised the manuscript, and approved the final version. Eileen Rillamas-Sun contributed to the design of the statistical analysis and manuscript, performed data analysis, interpreted data, revised the manuscript, and approved the final version.

Sponsor's Role: The sponsors did not play a role in the analysis or preparation of this manuscript.

85 with functional independence relative to death before 85. Similar, but slightly weaker odds ratios were seen for survival to age 85 with disability vs. death before age 85. Better kidney function was not significantly associated with survival to age 85 with independent function when compared to women surviving *with* disability.

CONCLUSION—Better kidney function was associated with survival to age 85 with and without disability, as compared to death before age 85.

Keywords

eGFR; disability; physical function; successful aging

INTRODUCTION

The number of adults over age 85 in the United States is expected to triple by the year 2050, totaling more than 18 million.¹ This expanding “oldest old” demographic highlights the importance of understanding how to remain healthy, physically and mentally active, and disability-free in advanced years. While chronic disease and disability prevalence rates are high in older adults, some adults live to late-age without major disabling health issues.^{2–4} This subset of the population may provide valuable information about the factors predicting survival and intact functioning in later life.

Impaired physical function, including limitations in mobility and activities of daily living (ADLs), can greatly affect quality of life for older adults and the prospects of remaining independent. Chronic kidney disease (CKD) is a well-established risk factor for mortality,^{5–7} but emerging evidence suggests reduced kidney function also negatively impacts physical function and aging success.^{8–14} Mild reductions in kidney function have been associated with poorer performance in functional testing, including reduced muscle strength and slower walking speeds.^{8,9} In several prospective studies, impaired kidney function has been associated with subsequent functional limitations and disability in community-dwelling older populations.^{10–12} In the Health, Aging, and Body Composition study, reduced kidney filtration was associated with increased risk of developing mobility limitations during the 4½-year follow-up period.¹⁰ Similarly, in a 6-year longitudinal analysis of the Cardiovascular Health Study, poorer kidney function was associated with a reduction in years of life free of disability and major chronic health disease.¹¹

Impaired kidney function, a strong predictor of mortality in older adults,^{5–7} may also negatively impact physical function with aging.^{8–14} Currently, the role of kidney function in predicting functional independence in late-age survival is not known. The purpose of this study was to assess the relationship of kidney function with disability-free survival to age 85 in a large prospective cohort of community-dwelling postmenopausal women.

METHODS

Study Population

This analysis included postmenopausal women from the Women’s Health Initiative (WHI) program enrolled in either the WHI Observational Study (OS) or Clinical Trials (CT).

Details about the study have been previously published.^{15,16} Briefly, 40 US clinical centers recruited 161,808 postmenopausal women, aged 50–79, between October 1993 and December 1998. Institutional review boards at participating institutions approved study protocols. Each study participant provided written informed consent. Health information was updated annually for women in the OS and semiannually for women in the CT by mail and/or telephone questionnaires through 2005. Women surviving in 2005 were recruited for an extension study from 2005–2010; 76.9% of 150,075 eligible women consented to participate. A second extension study followed from 2010–2015; 86.8% of 107,706 eligible women consented to participate. Women enrolled in the extension studies were followed annually through mailed questionnaires for health updates, changes in functional status, and death.

WHI participants who were born before September 1, 1928 and therefore had the potential to survive to their 85th birthday by August 31, 2013 were included in this study population (See Figure 1). Cardiovascular disease (CVD) biomarkers were assessed in a subcohort of WHI participants selected to be representative of WHI Hormone Therapy (HT) Trials participants, with inclusion of all eligible Hispanic and African American women and a comparable group of non-minority HT participants matched on age, hysterectomy status, and date of enrollment. In total, 8,815 African Americans, 3,642 Hispanics, and 10,306 European Americans had serum samples collected. Women without baseline serum creatinine measurements (n=43,555) and women with baseline mobility or ADL disability (n=270) were excluded from this analysis. To prevent misclassification of survival with functional independence, women without a completed questionnaire assessing mobility and ADL independence within one year of turning age 85 were also excluded from the analyses (n=1,435). After these exclusions, 7,178 women remained in the analytic study population.

Classification of Function and Disability

Women were assessed for incident disability or death from study baseline through September 2013 for this analysis. Follow-up time for study participants ranged from <1–19 years, with a median of 15 years. WHI participants were contacted annually or semi-annually to ascertain medical updates. Typically, a family member of a participant who died returned the mailed survey form to notify study personnel of the death. When participant or proxy information was not received, searches of the National Death Index and obituary notices were performed.

Disability status was determined through mailed surveys collecting self-reported physical function. For OS participants, disability was assessed at baseline and three years after baseline. For CT participants, disability was assessed at baseline, one year after baseline, and at study close. In a subset of CT participants, disability measures were collected every three years until study close. Disability was then evaluated annually for participants enrolled in the extension studies. Reporting was performed by proxy when a participant's illness or disability prevented her from completing the questionnaire independently. Women who reported using a walker, crutches, or a wheelchair to move on a level surface or who responded that their health greatly limited their ability to walk one block or climb one flight of stairs were categorized with mobility disability. Women who reported inability to eat,

dress, get in and out of bed, or take a bath/shower independently were classified with ADL disability. Women who lived to age 85 but reported either mobility or ADL disability prior to reaching age 85 were categorized as surviving to 85 with disability (n=1798). Women who survived to age 85 without ever reporting mobility or ADL disability were categorized as surviving with functional independence (n=3155). Measures of disability within one year of reaching age 85 were required for classification of functional independence.

Laboratory Methods

A 12-hour fasting serum sample was obtained during the baseline exam, processed and stored at -70°C according to strict quality control procedures. Stored frozen serum specimens were sent to the University of Minnesota Fairview laboratory for assay of biomarkers including total cholesterol, triglycerides, HDL, glucose, and C-reactive protein using standard laboratory methods (Roche Diagnostics, Indianapolis, IN 46250). Creatinine was assayed using the Creatinine Plus Reagent (Roche Diagnostics) on Roche Modular P Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN 46250). LDL concentration was calculated from total cholesterol, HDL and triglyceride concentrations using the Friedewald equation.¹⁷

Covariate Data Collection

Demographic and health information was collected using questionnaires at baseline clinic visits. Demographic information included age, race/ethnicity (White, Black/African American, Hispanic, American Indian/Alaskan Native, Asian/Pacific Islander), annual income (classified as $<\$20,000$, $\$20,000$ – $50,000$, or $>\$50,000$) and educational attainment (classified as less than high school, high school, some vocational/college education, or college graduate). Socioeconomic status was also assessed using a neighborhood socioeconomic status variable (NSES) based on 2000 census tract-level data on income, poverty, education, and other SES variables within geographical regions.¹⁸ Scores ranged from 0–100 with higher NSES scores indicating more affluent census tracts. Lifestyle and health behaviors were ascertained by questionnaire including alcohol consumption (frequency and amounts of wine, beer and hard liquor) and smoking status (current, past, non-smoker). Medical history at baseline was based on self-reported physician diagnosis of cardiovascular disease, diabetes, hypertension, congestive heart failure, or past cerebrovascular incident. Current prescription medications were ascertained by interviewers who recorded the names of medications directly from medication containers and entered these into the Medispan database.¹⁵ Analyses for this study included use of any anti-hypertensive medications and specifically the use of ACE inhibitors, due to potential influence on eGFR.

Trained clinic staff recorded blood pressure and anthropometric measurements at the baseline clinic visit. Blood pressure was measured in the right arm using a conventional mercury sphygmomanometer in a seated position after 5 minutes of rest. Two blood pressure measurements were taken at least 30 seconds apart, and the average was used for the current analyses. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Weight was measured to the nearest 0.1 kg on a balance beam scale with participant wearing light clothes without shoes. Body mass index (BMI) was calculated as weight in kilograms

divided by height in meters squared. BMI was categorized as underweight (<18.5), healthy weight (18 to <25), overweight (25 to <30), obese I (30 to <35), obese II (35 to <40), and obese III (≥40) using standard World Health Organization cut points.¹⁹ For stratification purposes, Obese I–Obese III were combined into one category.

Statistical Analysis

The primary exposure of interest was the estimated glomerular filtration rate (eGFR) based on serum creatinine measurements collected at baseline. eGFR was calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation²⁰ with the formula:

$$eGFR_{CKD-EPI_{cr}} = 141 \times \min(S_{cr}/0.7, 1)^{-0.329} \times \max(S_{cr}/0.7, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \times (1.159 \text{ if African American})$$

eGFR is expressed in mL per min per 1.73 m² of body surface area. Participants were divided into four eGFR strata: ≥90, 60–89, 45–59, and <45 mL/min/1.73m² according to 2012 Kidney Disease: Improving Global Outcomes (KDIGO) cut-points.²¹

Baseline demographic and health information were compared across levels of baseline kidney function and across outcomes. Pearson chi-square tests and analysis of variance were used to test for significant differences in categorical and continuous data, respectively.

Kaplan-Meier curves were plotted to visualize survival over time of women with eGFR stratified by ≥90, 60–89, 45–60, and <45. The association of kidney function with outcome was assessed by polychotomous logistic regression with 3 outcomes: surviving to age 85 with functional independence, surviving to age 85 with disability, and death before age 85 (reference). To determine odds of survival with functional independence versus survival with disability, disability at age 85 was assigned as the reference group. We used a series of nested models to explore potential confounders. An initial model adjusted for age and ethnicity. A fully adjusted model included all covariates significantly associated with kidney function and survival with functional independence, as well as biologically plausible potential confounders. Covariates not normally distributed were log-transformed. Because serum creatinine is influenced by muscle mass, multiplicative interaction terms between kidney function and BMI were added to the fully adjusted model to assess effect modification by BMI. Interactions were tested using indicator variables because of evidence of non-linearity in the associations being evaluated. A likelihood ratio test comparing the full and reduced models, with 18 degrees of freedom (4 categories of eGFR by 4 categories of BMI) was used to test the significance of interactions.

Two sensitivity analyses were performed to determine whether alternative adjustments for socioeconomic status changed the results. The first sensitivity analysis added the annual household income variable to the fully adjusted model. The second sensitivity analysis used NSES as an alternate to the education and income variables. NSES, which takes into consideration neighborhood-level characteristics including access to medical and social services, exposure to chronic environmental pollutants and stressors, and physical

accessibility and walkability of the environment, amongst other characteristics, may influence health and mortality risk differently than individual-level SES characteristics.^{18,22}

All analyses were completed using SAS statistical software, version 9.3 (SAS Institute Inc). A nominal p-value of < 0.05 was considered statistically significant.

RESULTS

Comparisons of baseline participant characteristics by kidney function are shown in Table 1. Statistically significant differences across levels of kidney function were observed for most baseline variables, with the exception of medication use and HDL levels. Women with poorest kidney function, eGFR <45 mL/min/1.73m², were more likely to have diagnoses of hypertension, CVD, congestive heart failure, and diabetes, and have higher blood pressure, C-reactive protein, cholesterol, and blood glucose levels at baseline.

Table 2 displays baseline characteristics according to aging outcome. Comparisons showed that participants who died before age 85 had a higher burden of CVD biomarkers and disease comorbidity at baseline. Levels of covariates tended to be intermediate in the group that survived with disability.

Survival curves for participants based on eGFR levels are displayed in Figure 2. Women with eGFR 60–89 mL/min/1.73m² had the highest proportion survival over time, with more than 72% surviving at 15 years follow-up. Women with eGFR <45 mL/min/1.73m² had significantly lower survival over time (p<.001) with less than 33% surviving at 15 years follow-up. In unadjusted polychotomous logistic regression, an inverted u-shaped association was observed between eGFR and odds of survival to 85, with or without disability, relative to death before age 85 (Table 3). In the unadjusted analyses, the highest odds ratios of survival were observed with eGFR 60–89 mL/min/1.73m² relative to the lowest eGFR category (OR=6.04, 95% CI 3.95–9.25 for functional independence; OR=4.45, 95% CI 2.73 – 7.24 for survival with disability). Weaker odds of survival were noted with women with the highest eGFR, ≥90 mL/min/1.73m², relative to lowest eGFR (OR=3.70, 95% CI, 2.40 – 5.72 for functional independence; OR = 4.01, 95% CI 2.44 – 6.59 for survival with disability). With full adjustment of confounders, odds of survival to 85 with independent function versus death before age 85 for eGFR categories of ≥90 and 68–90 mL/min/1.73m² were similar. Women with baseline eGFR ≥90 had 2.71 times (95% CI 1.62 – 4.51) and women with eGFR 60–89 had 3.04 times (95% CI 1.85 – 5.00) higher odds of surviving with independent function relative to death before 85, compared to women in the reference group, in the fully adjusted model. Similar, but somewhat weaker odds ratios were observed for kidney function categories when comparing women who survived to age 85 *with* disability to women who died before age 85 (Table 3).

When comparing surviving with functional independence relative to disability, higher eGFR was weakly and non-significantly associated with improved odds of functional independence, with odds ratios ranging from 1.18 (95% CI, 0.62–2.25) for eGFR ≥90 to 1.43 (95% CI, 0.73–2.80) for eGFR 45–59, in the fully adjusted model.

The association between kidney function and aging outcomes did not differ significantly by BMI ($p=0.55$). Sensitivity analyses showed no substantive differences in associations of kidney function with survival outcomes when the income variable was added to the fully adjusted model, nor when the NSES variable replaced the income and education variables.

DISCUSSION

Better kidney function was associated with increased odds of surviving to age 85 with functional independence relative to death before 85 in this community-dwelling population of postmenopausal women. Better kidney function was similarly associated with survival to age 85 *with* disability relative to death before age 85, although this association was slightly weaker. Better kidney function was predictive of survival to age 85, with or without disability, independent of cardiometabolic disease and CVD biomarkers. Although there was a trend towards higher odds of surviving to age 85 with functional independence when comparing to women who survived to age 85 *with* disability, none of the odds ratios were significantly different.

Women with kidney function above the cutpoint for CKD, 60 mL/min/1.73m^{2.23} demonstrated the greatest odds of surviving to age 85, with or without disability. Specifically, our results demonstrated the highest likelihood of survival to age 85 with eGFR 60–89 mL/min/1.73m². Consistent with others,^{5,7} we found creatinine-based eGFR 90 mL/min/1.73m² was not associated with better survival odds than eGFR of 60–89 mL/min/1.73m². While higher kidney filtration is likely advantageous for healthy aging, the highest eGFR categorization may also include women in a state of hyperfiltration and women with reduced muscle mass or malnutrition, contributing to a weakened odds of survival with functional independence, particularly in the unadjusted model. Hyperfiltration may occur in some older adults with diabetes and/or metabolic syndrome, and may be an initial step in the progression of nephropathy.^{24,25} Erroneous overestimates of kidney filtration rates can occur with conditions including sarcopenia, malnutrition, and/or frailty due to lower creatinine production.^{24,26} With full adjustment, a closer approximation of odds of survival with functional independence between the 90 and 60–89 eGFR groups was noted, yet a slightly lower odds ratio remained for women with the highest filtration rates.

Our findings reveal that women with better kidney function are more likely to survive to age 85, with or without disability, relative to death before age 85. However, baseline eGFR did not significantly predict surviving to age 85 disability-free compared to surviving with disability. There are several potential explanations for our findings. First, kidney function may not differentially predict disability with aging due to the heterogeneity of pathologies leading to disability at age 85. As an example, osteoarthritis is the most prevalent cause of disability in older adults²⁷ but osteoarthritis is not linked with kidney dysfunction. Second, we cannot exclude the possibility that use of serum creatinine for eGFR calculations may have reduced our ability to detect differences in odds of survival with and without disability. Although we adjusted for several confounders and assessed for interaction of kidney function and BMI, residual confounding by muscle mass, body size, and frailty may still remain, obscuring an association between kidney function and disability. In fact, in two previous studies, significant associations between frailty and kidney function were greatly

attenuated when creatinine-based eGFR was used instead of cystatin C-based calculations.^{13,14} Third, selective retention of healthier women in WHI who lived to age 85 irrespective of their disabilities may have reduced our ability to detect a significant difference in kidney function between the survivor groups with and without disability. WHI investigators have shown that women who remained in the study past their 80th birthday tended to be healthier than their counterparts who did not consent to the two extension study re-enrollment periods.²⁸

While this study found that poorer kidney function is a strong predictor of death prior to age 85, we could not assess the relationship of kidney function to time of incident disability. Due to few measurements of functional status prior to 2005, we are unable to determine if disability preceded death in our cohort of women who died before age 85. Prior longitudinal studies found poorer kidney function in community-dwelling older adults predicted incident disability over 4–6 years of follow-up.^{10,11} Mobility and ADL disability, strong risk factors for death,^{29,30} have been found to shorten life expectancy up to 10 years.³¹ Women with better kidney function may have greater resilience that extends their survival in spite of mobility and/or ADL disability as compared to women with poorer kidney function who develop disability.

Aligned with the latter explanation, consistent associations between poor kidney function, cardiovascular disease, and mortality have been firmly established, although the exact biological mechanisms remain undetermined. The kidneys may be particularly susceptible to damage from vascular stressors and thus serve as a sensitive marker of cardiovascular disease.³² Conversely, impaired kidney function resulting in improper fluid retention and filtration may lead to increased hemodynamic stress, hypertension, and elevated circulatory levels of inflammatory markers.^{33,34} Regardless of directionality of the relationship between cardiovascular impairment and kidney dysfunction, reduced kidney filtration, even at subclinical levels, may signal cellular and organ senescence and an increased rate of biological aging.³⁵ In proposed phenotypes for healthy aging, kidney function consistently serves as an integral component of physiologic health.^{36–38} Reduced kidney function may be indicative of cumulative “wear and tear” on the body and accelerated aging.³⁶ Kidney dysfunction, in turn, may lead to impaired regulation of electrolytes, inflammation, anemia, and insulin resistance, thus contributing to physiologic deterioration. It is not clear at this time if impaired kidney function directly contributes to accelerated aging or rather serves a marker of the severity of cumulative effects of clinical and subclinical disease morbidity. Therefore, at this time, it is uncertain if interventions to improve kidney function in older adults may protect the body from physiologic decline, but this potential clinical implication deserves further study.

There are several limitations in this study that warrant consideration. Our study population included only women, and it is unknown whether these results can be generalized to older men. However, in general, women tend to live longer than men, and findings that pertain to women’s aging hold inherent public health value. Our study used creatinine measures and other health characteristics collected at a single baseline visit. In this sample, alternate biomarkers of kidney function including urinary albumin levels or cystatin C were not available. As discussed previously, muscle mass influences creatinine, a well-known

limitation of using this biomarker. However, kidney function assessed using cystatin C in WHI women has also shown associations with BMI³⁹ and it is uncertain whether cystatin C is superior to serum creatinine in predicting mobility independence in late-age survival. Additionally, it should be recognized that serum creatinine remains the most commonly used biomarker for estimating GFR clinically. The analysis presented in this study is more directly translatable to geriatric clinical practice than use of cystatin C-based eGFR. Future studies comparing cystatin C and serum creatinine equations in assessing kidney function and mobility in late-age survival would be informative.

Our study has several strengths. It included a large sample of ethnically diverse, community dwelling, postmenopausal women from the well-characterized WHI Study. Participants were followed for an average of 13.5 years with a high retention rate. Detailed information on potential confounders and disease mediators were collected and analyzed. Our study had a substantially longer follow-up than previous studies examining eGFR and physical functioning, which allowed us to study the long-term health effects of kidney function.

In conclusion, better kidney function as measured by serum creatinine-based eGFR, was predictive of survival to age 85 with functional independence, and to a lesser extent survival to age 85 with disability, in postmenopausal community-dwelling women. Results of this study suggest that eGFR may be used as a clinical marker of prospects for longevity in older women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services (HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C).

Elements of Financial/ Personal Conflicts	Alyson Cavanaugh		Andrea Z. LaCroix		Donna Kritz-Silverstein		Eileen Rillamas-Sun		Dena E. Rifkin	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		X		X
Grants/Funds		X		X		X		X		X
Honoraria		X		X		X		X		X
Speaker Forum		X		X		X		X		X
Consultant		X		x		X		X		X
Stocks		X		X		X		X		X
Royalties		X		X		X		X		X
Expert Testimony		X		X		X		X		X
Board Member		X		X		X		X		X
Patents		X		X		X		X		X

Elements of Financial/ Personal Conflicts	Alyson Cavanaugh		Andrea Z. LaCroix		Donna Kritz-Silverstein		Eileen Rillamas-Sun		Dena E. Rifkin	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Personal Relationship		X		X		X		x		X

For “yes”, provide a brief explanation:

References

1. Ortman, Jennifer M., Velkoff, Victoria A., Hogan, Howard. An Aging Nation: The Older Population in the United States, Current Population Reports, P25-1140. U.S. Census Bureau; Washington, DC: 2014.
2. Shadyab AH, LaCroix AZ. Genetic factors associated with longevity: A review of recent findings. *Ageing Res Rev.* 2015; 19:1–7. DOI: 10.1016/j.arr.2014.10.005 [PubMed: 25446805]
3. Bell CL, Chen R, Masaki K, et al. Late-life factors associated with healthy aging in older men. *J Am Geriatr Soc.* 2014; 62(5):880–888. DOI: 10.1111/jgs.12796 [PubMed: 24779449]
4. Rillamas-Sun E, LaCroix AZ, Waring ME, et al. Obesity and late-age survival without major disease or disability in older women. *JAMA Intern Med.* 2014; 174(1):98–106. DOI: 10.1001/jamainternmed.2013.12051 [PubMed: 24217806]
5. Shlipak MG, Sarnak MJ, Katz R, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med.* 2005; 352(20):2049–2060. DOI: 10.1056/NEJMoa043161 [PubMed: 15901858]
6. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004; 351(13):1296–1305. DOI: 10.1056/NEJMoa041031 [PubMed: 15385656]
7. Shastri S, Katz R, Rifkin D. Kidney Function and Mortality in Octogenarians: Cardiovascular Health Study All Stars. *J Am Geriatr Soc.* 2012; 60(7):1201–1207. DOI: 10.1111/j.1532-5415.2012.04046.x.Kidney [PubMed: 22724391]
8. Odden MC, Chertow GM, Fried LF, et al. Cystatin C and measures of physical function in elderly adults: the Health, Aging, and Body Composition (HABC) Study. *Am J Epidemiol.* 2006; 164(12):1180–1189. DOI: 10.1093/aje/kwj333 [PubMed: 17035344]
9. Roshanravan B, Patel KV, Robinson-Cohen C, et al. Creatinine Clearance, Walking Speed, and Muscle Atrophy: A Cohort Study. *Am J Kidney Dis.* 2014; 65(5):737–747. DOI: 10.1053/j.ajkd.2014.10.016 [PubMed: 25542415]
10. Fried LF, Lee JS, Shlipak M, et al. Chronic kidney disease and functional limitation in older people: health, aging and body composition study. *J Am Geriatr Soc.* 2006; 54(5):750–756. DOI: 10.1111/j.1532-5415.2006.00727.x [PubMed: 16696739]
11. Sarnak MJ, Katz R, Fried LF, et al. Cystatin C and aging success. *Arch Intern Med.* 2008; 168(2):147–153. DOI: 10.1001/archinternmed.2007.40 [PubMed: 18227360]
12. Odden MC, Shlipak MG, Tager IB. Serum creatinine and functional limitation in elderly persons. *Journals Gerontol - Ser A Biol Sci Med Sci.* 2009; 64(3):370–376. DOI: 10.1093/gerona/gln037
13. Dalrymple LS, Katz R, Rifkin DE, et al. Kidney function and prevalent and incident frailty. *Clin J Am Soc Nephrol.* 2013; 8(12):2091–2099. DOI: 10.2215/CJN.02870313 [PubMed: 24178972]
14. Hart A, Paudel ML, Taylor BC, et al. Cystatin C and frailty in older men. *J Am Geriatr Soc.* 2013; 61(9):1530–1536. DOI: 10.1111/jgs.12413 [PubMed: 24001352]
15. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women’s Health Initiative study design. *Ann Epidemiol.* 2003; 13(9 Suppl):S5–S17. [Accessed February 3, 2015] <http://www.ncbi.nlm.nih.gov/pubmed/14575938>. [PubMed: 14575938]
16. Group TWHIS. Design of the Women’s Health Initiative clinical trial and observational study. The Women’s Health Initiative Study Group. *Control Clin Trials.* 1998; 19(1):61–109. [Accessed February 3, 2015] <http://www.ncbi.nlm.nih.gov/pubmed/9492970>. [PubMed: 9492970]

17. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972; 18(6):499–502. [Accessed September 18, 2014] <http://www.ncbi.nlm.nih.gov/pubmed/4337382>. [PubMed: 4337382]
18. Shih RA, Ghosh-Dastidar B, Margolis KL, et al. Neighborhood socioeconomic status and cognitive function in women. *Am J Public Health.* 2011; 101(9):1721–1728. DOI: 10.2105/AJPH.2011.300169 [PubMed: 21778482]
19. Consultation WE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet.* 2004; 363(9403):157–163. [PubMed: 14726171]
20. Levey AS, Stevens La, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009; 150(9):604–612. DOI: 10.7326/0003-4819-150-9-200905050-00006 [PubMed: 19414839]
21. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group KDIGO. 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013; 3:1–150.
22. Bird C, RASCE, et al. Neighborhood socioeconomic status and incident coronary heart disease among women. *J Gen Intern Med.* 2009; 24(suppl 1):S127.
23. Eckardt KU, Berns JS, Rocco MV, Kasiske BL. Definition and Classification of CKD: The Debate Should Be About Patient Prognosis-A Position Statement From KDOQI and KDIGO. *Am J Kidney Dis.* 2009; 53(6):915–920. DOI: 10.1053/j.ajkd.2009.04.001 [PubMed: 19406541]
24. Shastri S, Sarnak MJ. Chronic kidney disease: High eGFR and mortality: high true GFR or a marker of frailty? *Nat Rev Nephrol.* 2011; 7(12):680–682. DOI: 10.1038/nrneph.2011.153 [PubMed: 22009247]
25. Sasson AN, Cherney DZ. Renal hyperfiltration related to diabetes mellitus and obesity in human disease. *World J Diabetes.* 2012; 3(1):1–6. DOI: 10.4239/wjd.v3.i1.1 [PubMed: 22253940]
26. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. *N Engl J Med.* 2006; 354(23):2473–2483. DOI: 10.1056/NEJMra054415 [PubMed: 16760447]
27. Brault MW, Hootman J PhD, Helmick CG MD, Theis KAM. US Census Bureau. Prevalence and Most Common Causes of Disability Among Adults --- United States, 2005. *MMWR Morb Mortal Wkly Rep.*
28. Beavers DP, Pettinger M, Leng X, Tindle HA. The Evolution of the WHI 80+ Cohort. *J Gerontol A Biol Sci Med Sci.* 2016; 71(S1):S13–S22. DOI: 10.1093/gerona/glv050 [PubMed: 25922347]
29. Tiainen K, Luukkaala T, Hervonen A, Jylhä M. Predictors of mortality in men and women aged 90 and older: A nine-year follow-up study in the Vitality 90+ study. *Age Ageing.* 2013; 42(4):468–475. DOI: 10.1093/ageing/aft030 [PubMed: 23486170]
30. Keeler E, Guralnik JM, Tian H, Wallace RB, Reuben DB. The impact of functional status on life expectancy in older persons. *Journals Gerontol - Ser A Biol Sci Med Sci.* 2010; 65 A(7):727–733. DOI: 10.1093/gerona/gfq029
31. Majer IM, Nusselder WJ, Mackenbach JP, Klijs B, Van Baal PHM. Mortality risk associated with disability: A population-based record linkage study. *Am J Public Health.* 2011; 101(12):9–15. DOI: 10.2105/AJPH.2011.300361
32. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney Disease as a Risk Factor for Development of Cardiovascular Disease: A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation.* 2003; 108(17):2154–2169. DOI: 10.1161/01.CIR.0000095676.90936.80 [PubMed: 14581387]
33. Shlipak MG, Fried LF, Crump C, et al. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation.* 2003; 107(1):87–92. DOI: 10.1161/01.CIR.0000042700.48769.59 [PubMed: 12515748]
34. Knight EL, Rimm EB, Pai JK, et al. Kidney dysfunction, inflammation, and coronary events: a prospective study. *J Am Soc Nephrol.* 2004; 15(7):1897–1903. DOI: 10.1097/01.ASN.0000128966.55133.69 [PubMed: 15213279]

35. Yang H, Fogo AB. Cell senescence in the aging kidney. *J Am Soc Nephrol*. 2010; 21(9):1436–1439. DOI: 10.1681/ASN.2010020205 [PubMed: 20705707]
36. Sanders JL, Minster RL, Barnada MM, et al. Heritability of and mortality prediction with a longevity phenotype: The healthy aging index. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2014; 69(4):479–485. DOI: 10.1093/gerona/glt117
37. Sanders JL, Boudreau RM, Penninx BW, et al. Association of a modified physiologic index with mortality and incident disability: the health, aging, and body composition study. *Journals Gerontol Ser A Biol Sci Med Sci*. 2012; 67(12):1439–1446. doi:<http://dx.doi.org/10.1093/gerona/gls123>.
38. Walter S, MacKenbach J, Vokó Z, et al. Genetic, physiological, and lifestyle predictors of mortality in the general population. *Am J Public Health*. 2012; 102(4):3–11. DOI: 10.2105/AJPH.2011.300596
39. LaCroix AZ, Lee JS, Wu L, et al. Cystatin-C, renal function, and incidence of hip fracture in postmenopausal women. *J Am Geriatr Soc*. 2008; 56(8):1434–1441. DOI: 10.1111/j.1532-5415.2008.01807.x [PubMed: 18662213]

Figure 1.
Flow chart

Figure 2.
Survival probability over time by baseline eGFR

Table 1
Baseline characteristics of participants by kidney function;^a Women's Health Initiative, 1993–1998 (n=7178)

Characteristic	eGFR < 45	eGFR 45–59	eGFR 60–89	eGFR 90	p-value ^b
No. (%) of women	146 (2.0)	626 (8.7)	4775 (66.5)	1631 (22.7)	
Age, years, mean (SD)	72.41 (3.3)	72.7 (4.3)	72.0 (3.1)	70.2 (2.8)	<.001
Race/ethnicity					<.001
White	67 (45.9)	404 (64.5)	3667 (76.8)	914 (56.0)	
Black/African American	67 (45.9)	166 (26.5)	776 (16.3)	562 (34.5)	
Hispanic	7 (4.8)	43 (6.9)	269 (5.6)	131 (8.0)	
American Indian/Alaskan Native	5 (3.4)	13 (2.1)	63 (1.3)	24 (1.5)	
Income					<.001
<\$20,000	82 (58.2)	231 (38.3)	1462 (31.4)	547 (34.4)	
\$20,000 to \$50,000	47 (33.3)	258 (42.7)	2285 (49.1)	769 (48.4)	
>\$50,000	12 (8.5)	115 (19.0)	911 (19.6)	274 (17.2)	
Education					<.001
Less than high school	32 (22.4)	85 (13.7)	375 (7.9)	164 (10.1)	
High school	27 (18.9)	113 (18.2)	935 (19.7)	314 (19.3)	
Some vocational or college	55 (38.5)	224 (36.1)	1883 (39.7)	612 (37.7)	
College graduate	29 (20.3)	199 (32.1)	1548 (32.7)	534 (32.9)	
Smoking behavior					<.001
Never smoked	72 (51.8)	352 (57.5)	2637 (56.0)	833 (52.3)	
Past smoker	55 (39.6)	217 (35.5)	1827 (38.8)	616 (38.6)	
Current smoker	512(8.6)	43 (7.0)	245 (5.2)	145 (9.1)	
Alcohol intake					<.001
Never drinker	31 (21.7)	107 (17.4)	610 (12.9)	221 (13.7)	
Past drinker	55 (38.5)	167 (27.2)	970 (20.5)	427 (26.5)	
Drink 7 drinks/week	49 (34.3)	283 (46.0)	2613 (55.2)	786 (48.8)	
Drink > 7 drinks/week	8 (5.6)	58 (9.4)	439 (11.4)	176 (10.9)	
Diabetes, (% yes)	38 (26.4)	76 (12.1)	355 (7.4)	219 (13.4)	<.001
Hypertension, (% yes)	117 (81.8)	371 (60.0)	1972 (41.8)	693 (43.1)	<.001
Cardiovascular disease, (% yes)	61 (44.9)	172 (29.2)	923 (20.8)	293 (19.8)	<.001

Characteristic	eGFR < 45	eGFR 45–59	eGFR 60–89	eGFR 90	p-value ^b
History of CVA, (% yes)	21 (14.4)	44 (7.0)	200 (4.2)	57 (3.5)	<.001
Congestive heart failure, (% yes)	7 (4.8)	19 (3.0)	55 (1.2)	20 (1.2)	<.001
Use of ACE inhibitors, (% yes)	9 (6.3)	21 (3.6)	170 (3.9)	71 (4.7)	0.24
Any anti-hypertensive medication use (% yes)	14 (9.9)	46 (7.9)	298 (6.8)	124 (8.2)	0.14
Body mass index, kg/m ²					<.001
Underweight (<18.5)	1 (0.7)	4 (0.7)	29 (0.6)	15 (0.9)	
Normal weight (18.5 to <25)	19 (13.0)	135 (21.8)	1391 (29.3)	439 (27.1)	
Overweight (25 to 30)	59 (40.4)	247 (39.9)	1782 (37.6)	571 (35.2)	
Obese I (30 to <35)	36 (24.7)	148 (23.9)	1039 (21.9)	397 (24.5)	
Obese II (35 to 40)	23 (15.8)	59 (9.5)	375 (7.9)	144 (8.9)	
Obese III (40)	8 (5.5)	26 (4.2)	129 (2.7)	57 (3.5)	
SBP, mm Hg, mean (SD)	140.6 (20.9)	136.0 (18.6)	133.8 (18.0)	134.3 (17.8)	<.001
DBP, mm Hg, mean (SD)	73.8 (10.2)	74.3 (9.5)	74.5 (9.4)	75.2 (9.5)	0.03
LDL, mg/dL, mean (SD)	160.9 (47.0)	154.6 (40.9)	152.1 (35.5)	146.9 (35.1)	<.001
HDL, mg/dL, mean (SD)	54.2 (18.6)	53.3 (13.6)	54.0 (12.9)	54.5 (13.8)	0.23
Total cholesterol, mg/dL, mean (SD)	247.5 (54.9)	237.6 (45.6)	234.0 (39.2)	228.1 (38.9)	<.001
C-reactive protein, mg/L, mean (SD)	4.6 (5.9)	4.2 (6.5)	5.0 (7.2)	10.6 (34.8)	<.001
Triglycerides, mg/dL, mean (SD)	135.9 (94.0)	140.4 (75.0)	150.4 (87.6)	168.7 (86.1)	<.001
Glucose, mg/dL, mean (SD)	114.7 (38.3)	105.1 (31.3)	100.9 (27.0)	106.6 (37.1)	<.001

All values presented are No. (%) unless otherwise stated.

Abbreviations: eGFR, estimated glomerular filtration rate; CKD-EPI; Chronic Kidney Disease Epidemiology Collaboration formula; SD, standard deviation; CVA cerebrovascular accident; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein

^adetermined by eGFRCKD-EPI formula and expressed in mL/min/1.73m²

^bp=values determined by chi-square test for categorical data and ANOVA for continuous data.

Table 2
Baseline characteristics of participants by survival outcome: Women's Health Initiative, 1993–1998 (n= 7178)

Characteristic	Survival to age 85		Did not live to age 85	p-value ^a
	Free of disability	With disability		
No. (%) of women	3155 (44.0)	1798 (25.0)	2225 (31.0)	
Age, years, mean (SD)	72.4 (3.2)	70.8 (3.0)	71.4 (3.2)	<.001
Race/ethnicity				<.001
White	2392 (75.8)	1274 (70.9)	1386 (62.3)	
Black/African American	556 (17.6)	373 (20.8)	642 (28.9)	
Hispanic	176 (5.6)	126 (7.0)	148 (6.7)	
American Indian/Alaskan Native	31 (1.0)	25 (1.4)	49 (2.2)	
Annual family income				<.001
<\$20,000	799 (25.9)	627 (35.7)	896 (41.6)	
\$20,000 to \$50,000	1565 (50.7)	832 (47.4)	962 (44.5)	
>\$50,000	721 (23.4)	296 (16.9)	295 (13.7)	
Education				<.001
Less than high school	188 (6.0)	187 (10.4)	330 (14.8)	
High school	577 (18.3)	387 (21.5)	425 (19.1)	
Some vocational or college	1258 (39.9)	660 (36.7)	856 (38.5)	
College graduate	1132 (35.9)	564 (31.4)	614 (27.6)	
Smoking behavior				<.001
Never smoked	1880 (60.2)	979 (55.8)	1035 (47.5)	
Past smoker	1132 (36.3)	701 (39.9)	882 (40.5)	
Current smoker	109 (3.5)	75 (4.3)	261 (12.0)	
Diabetes (% yes)	129 (4.1)	199 (11.1)	460 (16.2)	<.001
Hypertension (% yes)	1159 (37.1)	831 (46.8)	1163 (53.1)	<.001
Cardiovascular disease (% yes)	482 (16.5)	358 (21.7)	609 (29.5)	<.001
History of CVA (% yes)	84 (2.7)	84 (4.7)	156 (7.0)	<.001
Congestive Heart Failure (% yes)	20 (0.6)	23 (1.3)	58 (2.6)	<.001
Use of ACE inhibitors (% yes)	116 (4.0)	78 (4.6)	77 (3.8)	0.474
Any anti-hypertensive medication (% yes)	204 (7.0)	137 (8.0)	141 (6.9)	0.377

Characteristic	Survival to age 85		Did not live to age 85	p-value ^a
	Free of disability	With disability		
Body mass index, kg/m ²				<.001
Underweight (<18.5)	18 (0.6)	6 (0.3)	25 (1.1)	
Normal weight (18.5 to <25)	1079 (34.4)	338 (18.9)	567 (25.7)	
Overweight (25 to <30)	1294 (41.2)	594 (33.2)	771 (35.0)	
Obese I (30 to <35)	575 (18.3)	526 (29.4)	519 (23.5)	
Obese II (35 to <40)	133 (4.2)	243 (13.6)	225 (10.2)	
Obese III (40)	42 (1.3)	80 (4.5)	98 (4.4)	
Systolic blood pressure, mmHg, mean (SD)	133.1 (17.8)	133.6 (17.8)	136.3 (18.5)	<.001
Diastolic blood pressure, mmHg, mean (SD)	74.3 (9.3)	74.9 (9.6)	74.8 (9.6)	<.001
Estimated glomerular filtration rate (eGFR) based on serum creatinine (mL/min/1.73m ²)				<.001
90	600 (19.0)	464 (25.8)	567 (25.5)	
60–89	2269 (71.9)	1192 (66.3)	1314 (59.1)	
45–59	258 (8.2)	122 (6.8)	246 (11.1)	
<45	28 (0.9)	20 (1.1)	98 (4.4)	
Low density lipoprotein, mg/dL, mean (SD)	152.7 (35.8)	150.0 (34.4)	150.3 (38.3)	<.001
High density lipoprotein, mg/dL, mean (SD)	55.5 (13.3)	52.8 (13.1)	53.0 (13.4)	<.001
Total cholesterol, mg/dL, mean (SD)	234.9 (39.4)	232.3 (38.8)	231.7 (42.4)	<.001
C-reactive protein, mg/L, mean (SD)	3.6 (5.7)	4.9 (7.5)	5.5 (10.9)	<.001
Triglycerides, mg/dL, mean (SD)	135.1 (81.2)	147.2 (79.1)	143.7 (82.4)	<.001
Glucose, mg/dL, mean (SD)	97.6 (20.0)	104.0 (30.9)	109.3 (39.4)	<.001

All values presented are No. (%) unless otherwise stated

Abbreviations: SD, standard deviation; CVA cerebrovascular accident

^a p=values determined by chi-square test for categorical data and ANOVA for continuous data.

Table 3

Association of survival with independent function, survival with disability, and death before age 85 according to baseline kidney function^a

	Baseline eGFR (in mL/min/1.73 m ²)			
	<45	45–59	60–89	90
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Odds of survival with functional independence^b / death before age 85				
Unadjusted	1.0 (reference)	3.67 (2.33 – 5.79)	6.04 (3.95 – 9.25)	3.70 (2.40 – 5.72)
Adjusted for demographics ^c	1.0 (reference)	3.74 (2.29 – 6.11)	5.91 (3.82 – 9.12)	4.91 (3.14 – 7.67)
Adjusted for confounders ^d	1.0 (reference)	2.22 (1.31 – 3.76)	3.04 (1.85 – 5.00)	2.71 (1.62 – 4.51)
Odds of survival with disability / death before age 85				
Unadjusted	1.0 (reference)	2.43 (1.43 – 4.12)	4.45 (2.73 – 7.24)	4.01 (2.44 – 6.59)
Adjusted for demographics ^c	1.0 (reference)	2.21 (1.30 – 3.75)	3.74 (2.29 – 6.12)	3.33 (2.02 – 5.50)
Adjusted for confounders ^d	1.0 (reference)	1.55 (0.87 – 2.74)	2.58 (1.52 – 4.38)	2.29 (1.33 – 3.94)
Odds of survival with functional independence^b / survival to age 85 with disability				
Unadjusted	1.0 (reference)	1.51 (0.82 – 2.79)	1.36 (0.76 – 2.42)	0.92 (0.51 – 1.66)
Adjusted for demographics ^c	1.0 (reference)	1.61 (0.86 – 2.99)	1.59 (0.88 – 2.84)	1.47 (0.81 – 2.68)
Adjusted for confounders ^d	1.0 (reference)	1.43 (0.73 – 2.80)	1.18 (0.63 – 2.22)	1.18 (0.62 – 2.25)

Abbreviations: eGFR, estimated glomerular filtration rate; OR, odds ratio; CI, confidence interval;

^aPolychotomous logistic regression with 3 outcomes; survival to age 85 with functional independence, survival to age 85 with disability, and death before age 85

^bDefined as survival to age 85 without disability

^cadjusted for age and race, n=7178

^dadjusted for age, race, education, smoking status, alcohol, BMI, diagnosis of hypertension, diabetes, cardiovascular disease, congestive heart failure, prior CVA, LDL, HDL, glucose, log triglycerides, log C-reactive protein, SBP, DBP, n=6243