Subclinical Vascular Disease Burden and Longer Survival

Citation	Odden, M. C., Yee, L. M., Arnold, A. M., Sanders, J. L., Hirsch, C., deFilippi, C., ... & Newman, A. B. (2014). Subclinical Vascular Disease Burden and Longer Survival. Journal of the American Geriatrics Society, 62(9), 1692-1698. doi:10.1111/jgs.13018
DOI	10.1111/jgs.13018
Publisher	John Wiley & Sons, Inc.
Version	Accepted Manuscript
Terms of Use	http://cdss.library.oregonstate.edu/sa-termsofuse

Subclinical Vascular Disease Burden and Longer Survival

Michelle C. Odden, PhD[1], Laura M. Yee, MS[2], Alice M. Arnold, PhD[2], Jason L. Sanders, PhD, MD[3], Calvin Hirsch, MD[4], Christopher deFilippi, MD[5], Jorge R. Kizer, MD, MSc[6], Marco Inzitari, MD[7], Anne B. Newman, MD, MPH[3]

[1]School of Biological and Population Health Sciences, Oregon State University, Corvallis, OR, [2]Department of Biostatistics, University of Washington, Seattle, WA, [3]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, [4]Departments of Medicine and Public Health Sciences, University of California, Davis, Medical Center, Sacramento, CA, [5]Division of Cardiovascular Medicine, University of Maryland, Baltimore, MD, [6]Department of Medicine, and Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, [7]Institute on Aging of the Universitat Autònoma de Barcelona, Barcelona, Spain

Corresponding Author:

Michelle C. Odden, PhD

Oregon State University

141B Milam Hall

Corvallis, OR, 97331

Ph: 541-737-3184, Fax: 541-737-6914

Email: Michelle.Odden@oregonstate.edu

This research was supported by AG023629 from the National Institute on Aging (NIA). Support for the CHS was provided by contracts HHSN268201200036C, HHSN268200800007C, N01 HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grant HL080295 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/PI.htm.

Dr. Odden is supported by the American Heart Association Western States Affiliate (11CRP7210088) and the National Institute on Aging (K01AG039387). Dr. Newman is supported by the University of Pittsburgh Claude D. Pepper Older Americans Independence Center P30AG024827, and the CHS All Stars NIA R01 (AG023629).

Running Head: Subclinical Vascular Disease and Survival

STRUCTURED ABSTRACT:

OBJECTIVES: Subclinical vascular disease (SVD) contributes to the aging process and may decrease life expectancy. We aimed to determine the contribution of gradations of SVD to the likelihood of achieving longer survival, and to determine what allows some individuals to achieve longer survival in the presence of high SVD.

DESIGN: Cohort Study

SETTING: Cardiovascular Health Study

PARTICIPANTS: Adults who were born after June 30th, 1918 and before June 30th, 1921 (n=2,082); participants were age 70-75 years at baseline visit (1992-1993).

MEASUREMENTS: A SVD index was scored as 0, 1, or 2 for no, mild, or severe abnormalities on ankle-arm index, electrocardiogram, and common carotid intima-media thickness measured at baseline. Survival groups were categorized as <80, 80-84, 85-89, and 90+ years.

RESULTS: A one point lower SVD score was associated with a 1.22 (95% confidence interval: 1.14, 1.31) higher odds of achieving longer survival, independent of potential confounders. This association was unchanged after adjustment for intermediate incident cardiovascular events. There was suggestion of an interaction of kidney function, smoking, and CRP with SVD; the association of SVD and longer survival appeared modestly increased in persons with poor kidney function, inflammation, or a history of smoking.

CONCLUSION: A lower burden of SVD is associated with longer survival, and this association was independent of intermediate cardiovascular events. Abstinence from smoking, better kidney function, and lower inflammation may attenuate the effects of higher SVD and further promote longer survival.

Key Words: survival, subclinical disease, cardiovascular disease, kidney function, smoking, inflammation

INTRODUCTION

Subclinical vascular disease (SVD), which may never cross the threshold of clinically recognized disease, contributes to health status and can increase the risk of disability and death.(1) Although it is accepted that high SVD is associated with morbidity and mortality,(2) whether low SVD is associated with longer survival has not been adequately described. The majority of research on determinants of longer survival has examined traditional risk factors and lifestyle factors, and has not included subclinical disease.(3-5) Subclinical changes may help explain the wide range in survival observed in aging that is not completely explained by clinically recognized disease.

In the Cardiovascular Health Study (CHS), we have observed the phenomenon of persons in whom subclinical and clinical vascular disease accumulates well beyond the threshold for high risk, yet such individuals continue to survive to very old age. By describing the characteristics of these individuals, we may identify factors that could modify the potential harm of SVD. It is these protective factors that may provide the most advantageous foundation for crafting interventions to promote longer survival, because they may decrease risk of disability and death even in high-risk individuals.

We examined if gradations of SVD are associated with longer survival, assessed by survival to age ≤80, 81-84, 85-89, and 90+ years. We evaluated this association in CHS participants born from June 30th, 1918 to June 30th, 1921, therefore including persons old enough at baseline to have achieved survival to age 90 or older by the end of follow-up. Age at death is associated with both the age at the time of risk factor measures, as well as birth cohort; therefore, additionally, these birth year restrictions minimized any confounding by these factors. In addition, we aimed to explore risk and protective factors in persons with a high burden of

SVD and longer survival. Our goal was to identify factors that modified the association between SVD and longer survival. Finally, we aimed to examine if the association of SVD and longer survival was mediated by intermediate cardiovascular disease (CVD) events.

METHODS

Study Population

The CHS is a community-based study of black and white adults aged ≥ 65 years at baseline. The primary aim of the CHS is to evaluate risk factors for the development and progression of cardiovascular disease in older adults (6). The study recruited persons from Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania in 1989-1990. Black participants were actively recruited during a supplemental enrollment process of CHS during 1992-1993; they constitute 15% of CHS participants. To be considered eligible, persons had to meet the following criteria: 1) age > 65 years; 2) not institutionalized; 3) expected to remain in the current community for 3 years or longer; 4) not under active treatment for cancer; and 5) provided informed consent without requiring a proxy respondent.

Participants were included in this study if they were born after June 30th, 1918 and before June 30th, 1921, which ensured participants were <75 years in 1992-93 (baseline for this analysis) and had an opportunity to reach age 90 by 2011, respectively. These birth year restrictions minimized any confounding by age and birth cohort. There were 2,082 participants who were born after June 30th, 1918 and before June 30th, 1921 and 1,584 had died by Dec 31st, 2011.

Deaths were identified by a review of obituaries, medical records, death certificates, and the Centers for Medicare and Medicaid Services health care–utilization database for

hospitalizations and from household contacts; 100% follow-up for ascertainment of mortality status was achieved.

Survival Group

Survival group was defined as an individual's maximum life span, determined by their age at death, if deceased, or by their calculated age as of Dec 31, 2011. Survival group was categorized into four groups for analysis: ≤80 years (n=504), 81-84 years (n=356), 85-89 years (n=525), or ≥90 years (n=697).

Subclinical Vascular Disease

The SVD index was assessed by the same method as in a previous CHS publication (2); this index better captures low levels of disease and high vascular health compared with traditional indices that only capture high levels of disease. Briefly, three measures of subclinical vascular health were assessed at the 1992-1993 visit: ankle-arm index (AAI), electrocardiogram (ECG), and common carotid ultrasound. Each measure was scored as 0, 1, or 2 indicating no, minor, or severe abnormalities. AAI was classified as low risk (>1.0 to 1.4), moderate risk (>0.9 to 1.0 or >1.4), high risk (≤0.9), based on previous research in the CHS.(7) ECG findings were classified based on standardized criteria in the CHS, and were categorized as no, minor (minor Q or QS waves, high R waves, minor isolated ST–T abnormalities, ST elevation, incomplete right bundle branch block, long QT interval, short PR, right axis deviation), or major abnormalities (ventricular conduction defects, major Q or QS abnormalities, minor Q or QS with ST–T wave abnormalities, left ventricular hypertrophy, isolated major ST–T, wave changes, atrial fibrillation or first-degree atrioventricular block).(8) Common carotid artery intima-media thickness (IMT) was classified as <0.905 mm, ≥0.905 mm to 1.218 mm to, or > 1.218 mm corresponding to the lowest quintile (most healthy), middle three quintiles, and upper quintile (least healthy).

Other Measures

Age was calculated as the difference between the visit date and the date of birth from the Medicare eligibility lists. Sex, education, and race were determined by self-report; race was categorized as black or white/other because <1% of participants self-identified as not of black or white race. Smoking history, alcohol consumption, and total physical activity (kcal/week) were assessed by standardized interview. Height, weight, and blood pressure were measured by standard protocol. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Total and high-density lipoprotein (HDL) cholesterol were measured in fasting blood samples. Diabetes was defined according to previous ADA guidelines as a fasting glucose ≥126 mg/dL or use of insulin or hypoglycemic medications, and impaired fasting glucose if glucose ≥110mg/dL and <126 mg/dL.(9) Cystatin C was measured by a BNII nephelometer (Seimens Healthcare Diagnostics, Deerfield, IL) that utilizes a particle enhanced immunonepholometric assay (N Latex Cystatin-C) (10). C-reactive protein (CRP) was measured in plasma by a high sensitive immunoassay. Depressive symptoms were assessed by a modified 10-item Center for Epidemiologic Studies Short Depression Scale (CES-D). Frailty was assessed by a modified scale which includes unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity, and has a more normalized distribution and less of a ceiling effect compared with the traditional Fried frailty index.(11, 12) Participants were asked about medication use and were asked to bring their medications to clinical visits.(13) Clinical cardiovascular disease was defined as a history of myocardial infarction, angina, revascularization, peripheral vascular disease, heart failure, transient ischemic attack, or stroke; CHS participants were classified at baseline by a combination of hospital records and physician

confirmation, and all incident events were adjudicated by a CHS outcome-assessment committee.(14)

Statistical Analysis

We described risk factors across survival groups and tested for linear trend. We compared the characteristics of participants with a higher burden of SVD (index score ≥4) who lived to age 85 or older (adapters) with those who died before age 85 (expected) using chi-squared tests for categorical risk factors and analysis of variance for continuous measures.

Ordered logistic regression models were used to assess the association between SVD (independent variable) and survival group (dependent variable), after adjustment for risk factors. This method estimates the proportional odds and assumes that the odds ratio is constant across any greater age groups, compared to any age group below (i.e. survival to ≥90 years versus <90 years, ≥85 years versus <85 years, or ≥80 years versus <80 years). The association was initially adjusted for clinical vascular disease status at baseline, age, sex and race. A fully adjusted model added education, alcohol consumption, alcoholic drinks in the last week, diabetes status (normal/IFG/diabetes), pack-years, BMI, ln(physical activity), systolic blood pressure, diastolic blood pressure, HDL cholesterol, total cholesterol, depressive symptoms, frailty score, ln(cystatin-C), ln(CRP), and use of aspirin or lipid lowering medications. We next examined whether adjustment for intermediate incident CVD events attenuated the association between SVD and longer survival, and we conducted the models of SVD and longer survival in persons free of CVD at baseline. Additionally we examine the association between SVD and the age at time of CVD event (≤75, 76-80, 81-84, 85+, never), also based on ordered logistic regression models. Models were assessed for violations of the proportional odds assumption. In order to determine whether other factors modified the risk of subclinical disease on longer survival, we

tested interactions of the subclinical disease index with the following *a priori* factors in the demographic-adjusted model: smoking status, physical activity, BMI, and frailty score, as well as those factors that differed across the adaptors and expected groups. Factors with interaction terms with a p-value of <0.1 were explored further in stratified models.

All analyses were conducted using Stata 11.0 (StataCorp, College Station, TX) and R 2.15 (The R Foundation, Vienna, Austria).

RESULTS

At the 1992-1993 visit, the mean age of the participants was nearly identical in women (72.7 [±1.5 years]) and men (72.8 [± 1.5]) years. By December 31st, 2011, 1,584 (76%) of the 2,082 participants had died; 504 (24%) participants lived to ≤80 years, 356 (17%) to 81-84 years, 525 (25%) to 85-89 years, and 697 (33%) to 90 years or older. The 498 surviving participants were aged 90-95, as determined by the birth cohort restrictions. On average, participants who achieved longer survival were less often male, had more education, were less likely to smoke, and had lower total pack years of smoking compared to those who died at younger ages. (Table 1) Those who achieved longer survival were likely to be more physically active, and have higher total and HDL cholesterol, and lower systolic blood pressure, CRP, and cystatin C levels. Participants reaching longer survival also had lower levels of depressive symptoms and frailty, and were more likely to be free of diabetes and CVD, and had lower rates of incident CVD. (Table 1)

Approximately 50% of people with no clinical or subclinical CVD, or a SVD index score of 1 lived to age 90 or older, whereas less than 20% of persons with a SVD score of ≥4 or clinical CVD achieved this milestone (Figure 1). Overall, there was a graded association between the level of SVD and the proportion of participants achieving longer survival ($p<0.01$ for all trends). Persons with no abnormalities on each of the component measures of SVD (AAI, ECG, common carotid IMT) were more likely to live to older age compared with persons with minor or severe abnormalities (Supplemental Table 1).

Persons with longer survival had a lower incidence rate of CVD events. (Figure 2) Persons achieving survival to age 90 and older had less than half the rate of incident CVD compared to those living to less than 80 years. There was an association between SVD and

incident rate of CVD, and the grade of the association was much stronger in those participants living to less than 80 years. (Figure 2)

We compared the characteristics of participants with a higher burden of SVD (index score ≥4) who lived to age 85 or older (adapters) and those who died before age 85 (expected) (Table 2). The adapters were less often men, were less likely to have ever smoked, and had fewer pack years of smoking. Adapters also had lower levels of cystatin C, depression, frailty, diabetes, and prevalent and incident CVD. (Table 2)

Based on a proportional odds model, the odds of achieving longer survival (≥90 years versus <90 years, ≥85 years versus <85 years, or ≥81 years versus <81 years) was 1.35 (95% CI: 1.27, 1.44) higher for each point lower of the SVD index. (Table 3) This estimate was nearly identical when we restricted the study population to those free of CVD at baseline (n=1,519): 1.34 (95% CI: 1.25, 1.45). The association of one point lower SVD and longer survival persisted after adjustment for potential confounders (OR = 1.22, 95% CI: 1.14, 1.31). (Table 3)Surprisingly, adjustment for intermediate CVD events did not affect the estimates for the associations of SVD and longer survival. (Table 3) Lastly, the association between a one point lower of the SVD index and age at incident CVD was 1.32 (95% CI: 1.21, 1.41) in demographic-adjusted models and 1.24 (95% CI: 1.14, 1.35) after adjustment for potential confounders.

The low risk group of each of the components of the SVD index was strongly and consistently associated with longer survival compared with the high risk group in demographic adjusted models. Supplemental Table 2) Adjustment for potential confounders had a modest impact on the estimates for the SVD measures, and rendered the moderate risk groups no longer statistically significantly different compared with the high risk groups.

Only ln(cystatin C) was observed to have a statistically significant interaction with SVD index score (p=0.04) in models adjusted for age, sex, race, and baseline CVD status. In persons with worse kidney function, the association of SVD index score and longer survival was modestly stronger. For example, among persons with a cystatin C of 1.0 mg/dL the odds ratio of a 1 point lower SVD index score was 1.31 (95% CI; 1.23, 1.41); whereas it was 1.75 (95% CI: 1.34, 2.27) in someone with a cystatin C of 2.72 mg/dL (one unit higher ln cystatin C). Additionally, there was a trend towards an interaction with smoking status (never vs. ever, p=0.07) and ln(CRP) (p=0.08); the association of SVD and longer survival appeared modestly stronger in persons with a history of smoking or higher levels of CRP. The odds ratio for a one point lower SVD index score among participants who never smoked was 1.25 (95% CI: 1.13, 1.38), versus 1.39 (95% CI: 1.29, 1.50) in those who smoked (Figure 2). The odds ratio for a one point lower SVD index score among participants with CRP of 1 mg/L was 1.25 (95% CI: 1.15, 1.37), whereas the odds ratio was 1.31 (95% CI: 1.23, 1.40) in participants with CRP of 2.72 mg/L (one unit higher ln CRP) . There was little evidence for effect modification by sex (p=0.83), physical activity (p=0.60), BMI (p=0.62), total cholesterol (p=0.29), frailty score (p=0.86), diabetes (p=0.11), or depression score (p=0.38).

DISCUSSION

This is the first large-scale study of SVD and years of survival; nearly 700 men and women in a narrow birth cohort window lived to age 90 years or older, offering a unique opportunity to evaluate factors that may enable elders to reach this age. In this investigation, we observed a strong and graded relationship between lower burden of SVD and longer survival. The three domains of the index – AAI, ECG, and common carotid IMT – capture different aspects of vascular disease which also increase with age (i.e. peripheral arterial disease, vessel wall stiffening, cardiac disease, arrhythmic disturbances, atherosclerosis), and were individually associated with longer survival. Although persons with greater SVD were more likely to have a clinical CVD event, this did not appear to mediate the relationship between SVD and longer survival. Additionally, there was modest evidence of a statistical interaction between kidney function, smoking, and inflammation and SVD on longer survival.

The present research used an index of subclinical vascular health that better captures low levels of disease and high vascular health compared with traditional indices that aim to capture disease.(2) Previously, Inzitari *et al*. reported a graded association between this index and survival, independent of demographics and traditional cardiovascular risk factors, as well as an association between the index and time to CVD event.(2) The current investigation extends this work to examine achievement of longer survival, as well as other characteristics that may augment or attenuate the damaging effects of SVD. The majority of prior literature on determinants of longer survival has focused on cardiovascular risk factors and genetic factors.(3, 4, 15-17) Subclinical disease may help explain the variability in survival in apparently healthy elders

Persons with longer survival were less likely to have prevalent CVD at age 70-75, and had lower rates of incident CVD prior to death. Although participants with higher SVD were more likely to progress to clinical CVD events, there was no evidence that this mediated the relationship between SVD and longer survival. Adjustment for intermediate CVD events had no impact on the association of SVD and longer survival. This suggests that high SVD reflects an increased physiologic burden that leads to earlier system failure, although this is not restricted to the CVD system. Due to the integrated function of the vascular system, higher SVD likely impairs function in a multitude of domains including musculoskeletal, renal, brain, and others.(18-22)

We observed several health factors that were different across persons with varying years of survival and a high burden of SVD. Persons with longer survival, despite a high burden of SVD, had a more favorable profile of smoking history, inflammation, kidney function, depressive symptoms, frailty, and diabetes. These findings are consistent with an investigation in the Physicians' Health Study. Yates *et al.* reported that smoking, sedentary lifestyle, diabetes, and other cardiovascular risk factors were associated with mortality before 90 years.(4) Physical activity was associated with longer survival in unadjusted analyses in the present study; however, it did not appear to be associated with longer survival among those participants with a high burden of SVD. We found the association of SVD and longer survival was weaker in those who abstained from smoking, had better kidney function, and lower inflammation. These factors have also been demonstrated to be associated with clinical CVD, and may be, in part, capturing the multifactorial process of vascular disease. (4, 23, 24) These results are consistent with the hypothesis that in persons with an unhealthy cardiovascular risk profile, low SVD may greatly contribute to the probability of achieving longer survival. In contrast, a good cardiovascular risk

profile explains much of the variance in years of survival, so the remaining variance due low SVD would be less, and therefore result in a weaker association between low SVD and longer survival. These findings suggest that these protective factors may be important targets for intervention, especially in persons who are the most vulnerable. While achieving therapeutic targets for multiple cardiovascular risk factors is paramount, our findings suggest that capitalizing on targeted opportunities for intervention may preserve health and extend years of survival.

Our study has limitations that should be considered. We restricted the study population to a birth cohort of CHS participants born after June 30th, 1918 and before June 30th, 1921. While these birth year restrictions minimized any confounding by age and birth cohort, this also limits the generalizability of the findings. Additionally, the differences we observed in risk and protective factors across adapters and those with expected years of survival were modest, and only the interaction between SVD and cystatin C reached statistical significance in models adjusted for age, sex, race, and baseline clinical CVD status. Interactions require more statistical power to identify with precision compared to main effects, and the increased variability of measures observed at older ages may further limit this power. The patterns observed are intriguing and should be further explored in other investigations, although we cannot exclude the possibility that these findings may have been due to chance.

In summary, we show that lower scores on a SVD index are associated with longer survival. Individuals who reach their 70's with a low burden of vascular disease are very likely to achieve survival to age 90. Clinically, they are good candidates for preventive measures targeting disability prevention, such as prevention of falls, fractures, cancer, arthritis, and dementia. Our study also suggests abstinence from smoking, better kidney function, and lower

inflammation may buffer the adverse effects of a high burden of vascular disease. Further investigations into factors that allow older adults to achieve exceptional health and longer survival in the presence of a high burden of disease will help guide the development of interventions which may be most beneficial for mitigating the effects of vascular disease and promoting long life.

ACKNOWLEDGMENTS

This research was supported by AG023629 from the National Institute on Aging (NIA). Support for the CHS was provided by contracts HHSN268201200036C, HHSN268200800007C, N01 HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grant HL080295 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/PI.htm.

Dr. Odden is supported by the American Heart Association Western States Affiliate (11CRP7210088) and the National Institute on Aging (K01AG039387). Dr. Newman is supported by the University of Pittsburgh Claude D. Pepper Older Americans Independence Center P30AG024827, and the CHS All Stars NIA R01 (AG023629).

None of the funding agencies had any role in the design and conduct of the study. The authors have no conflicts of interest to disclose

CONFLICT OF INTEREST

Elements of Financial/Personal Conflicts	Odden, M. C.		Yee, L.		Arnold, A. M.		Sanders, J. L.		Hirsch, C.		DeFilippi, C.	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		X		X		X
Grants/Funds		X		X		X		X		X		X
Honoraria		X		X		X		X		X		X
Speaker Forum		X		X		X		X		X		X

Consultant		X		X		X		X		X		X
Stocks		X		X		X		X		X		X
Royalties		X		X		X		X		X		X
Expert Testimony		X		X		X		X		X		X
Board Member		X		X		X		X		X		X
Patents		X		X		X		X		X		X
Personal Relationship		X		X		X		X		X		X

Elements of Financial/Personal Conflicts	**Kizer, J. R.**		**Inzitari, M.**		**Newman, A. B.**	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**
Employment or Affiliation		X		X		X
Grants/Funds		X		X		X
Honoraria		X		X		X
Speaker Forum		X		X		X
Consultant		X		X		X
Stocks		X		X		X
Royalties		X		X		X
Expert Testimony		X		X		X
Board Member		X		X		X
Patents		X		X		X
Personal Relationship		X		X		X

Author Contributions: Authors contributed to the following roles: study concept and design (MCO, AMA, CH, ABN), acquisition of subjects and/or data (AMA, CH, CD, ABN), analysis of data (LY, AMA), interpretation of data and results (MCO, LY, AMA, JLS, CH, CD, JRK, MI, ABN), preparation of manuscript (MCO, AMA, LY, ABN), and revision of manuscript (MCO, LY, AMA, JLS, CH, CD, JRK, MI, ABN).

Sponsor's Role: The sponsor had no role in the design or conduct of the study, analysis or interpretation of data, or preparation of the manuscript.

REFERENCES

1. Newman AB, Boudreau RM, Naydeck BL, et al. A physiologic index of comorbidity: relationship to mortality and disability. J Gerontol A Biol Sci Med Sci 2008;63(6):603-9.
2. Inzitari M, Arnold AM, Patel KV, et al. Subclinical vascular disease burden and risk for death and cardiovascular events in older community dwellers. J Gerontol A Biol Sci Med Sci 2011;66(9):986-93.
3. Stessman J, Hammerman-Rozenberg R, Cohen A, et al. Physical activity, function, and longevity among the very old. Arch Intern Med 2009;169(16):1476-83.
4. Yates LB, Djousse L, Kurth T, et al. Exceptional longevity in men: modifiable factors associated with survival and function to age 90 years. Arch Intern Med 2008;168(3):284-90.
5. Rajpathak SN, Liu Y, Ben-David O, et al. Lifestyle factors of people with exceptional longevity. J Am Geriatr Soc 2011;59(8):1509-12.
6. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. Annals of epidemiology 1991;1(3):263-76.
7. O'Hare AM, Katz R, Shlipak MG, et al. Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. Circulation 2006;113(3):388-93.
8. Furberg CD, Manolio TA, Psaty BM, et al. Major electrocardiographic abnormalities in persons aged 65 years and older (the Cardiovascular Health Study). Cardiovascular Health Study Collaborative Research Group. Am J Cardiol 1992;69(16):1329-35.
9. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20(7):1183-97.

10. Erlandsen EJ, Randers E, Kristensen JH. Evaluation of the Dade Behring N Latex Cystatin C assay on the Dade Behring Nephelometer II System. Scand J Clin Lab Invest 1999;59(1):1-8.

11. Sanders JL, Boudreau RM, Fried LP, et al. Measurement of organ structure and function enhances understanding of the physiological basis of frailty: the Cardiovascular Health Study. J Am Geriatr Soc 2011;59(9):1581-8.

12. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146-56.

13. Psaty BM, Lee M, Savage PJ, et al. Assessing the use of medications in the elderly: methods and initial experience in the Cardiovascular Health Study. The Cardiovascular Health Study Collaborative Research Group. J Clin Epidemiol 1992;45(6):683-92.

14. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. Ann Epidemiol 1995;5(4):278-85.

15. Hindorff LA, Rice KM, Lange LA, et al. Common variants in the CRP gene in relation to longevity and cause-specific mortality in older adults: the Cardiovascular Health Study. Atherosclerosis 2008;197(2):922-30.

16. Lescai F, Marchegiani F, Franceschi C. PON1 is a longevity gene: results of a meta-analysis. Ageing Res Rev 2009;8(4):277-84.

17. Reiner AP, Diehr P, Browner WS, et al. Common promoter polymorphisms of inflammation and thrombosis genes and longevity in older adults: the cardiovascular health study. Atherosclerosis 2005;181(1):175-83.

18. Rosano C, Kuller LH, Chung H, et al. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. J Am Geriatr Soc 2005;53(4):649-54.

19. Newman AB, Simonsick EM, Naydeck BL, et al. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. JAMA 2006;295(17):2018-26.

20. Newman AB, Gottdiener JS, McBurnie MA, et al. Associations of subclinical cardiovascular disease with frailty. J Gerontol A Biol Sci Med Sci 2001;56(3):M158-66.

21. Newman AB, Arnold AM, Naydeck BL, et al. "Successful aging": effect of subclinical cardiovascular disease. Arch Intern Med 2003;163(19):2315-22.

22. Brach JS, Solomon C, Naydeck BL, et al. Incident physical disability in people with lower extremity peripheral arterial disease: the role of cardiovascular disease. J Am Geriatr Soc 2008;56(6):1037-44.

23. Cushman M, Arnold AM, Psaty BM, et al. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: the cardiovascular health study. Circulation 2005;112(1):25-31.

24. 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):2049-60.

TABLES

Table 1. Characteristics of 2,082 participants from the Cardiovascular Health Study by survival group.

Survival Group (years)	<=80 (N= 504)	81-84 (N=356)	85-89 (N=525)	90+ (N=697)	
	Mean (± SD) or Median (IQR) or N (%)				p-value for trend
Age (years)	72.6 (± 1.4)	72.9 (± 1.5)	72.8 (± 1.5)	72.7 (± 1.5)	0.01
Male	251 (49.8%)	164 (46.1%)	217 (41.3%)	231 (33.1%)	<0.01
Black	75 (14.9%)	55 (15.4%)	67 (12.8%)	77 (11.0%)	0.13
Education					<0.01
Less than High School	166 (32.9%)	99 (27.8%)	125 (23.8%)	158 (22.7%)	
High School or GED	134 (26.6%)	105 (29.5%)	147 (28.0%)	217 (31.1%)	
College/Vocational	158 (31.3%)	120 (33.7%)	201 (38.3%)	244 (35.0%)	
Graduate/Professional	46 (9.1%)	32 (9.0%)	52 (9.9%)	78 (11.2%)	
Alcohol Consumption					0.67
None	287 (56.9%)	215 (60.4%)	283 (53.9%)	349 (50.1%)	
<7 drinks/wk	162 (32.1%)	97 (27.2%)	167 (31.8%)	259 (37.2%)	

	7-14 drinks/wk	20 (4.0%)	25 (7.0%)	44 (8.4%)	51 (7.3%)	
	>14 drinks/wk	35 (6.9%)	19 (5.3%)	31 (5.9%)	38 (5.5%)	
Smoking Status						<0.01
	Never	155 (30.8%)	132 (37.1%)	241 (45.9%)	384 (55.1%)	
	Former	257 (51.0%)	168 (47.2%)	239 (45.5%)	274 (39.3%)	
	Current	92 (18.3%)	56 (15.7%)	45 (8.6%)	39 (5.6%)	
Years Since Quit (Among Former Smokers)		18.6 (± 12.3)	22.0 (± 12.8)	22.9 (± 12.8)	25.3 (± 12.0)	<0.01
Pack Years		24.1 (0.0 - 49.4)	9.7 (0.0 - 34.4)	2.9 (0.0 - 27.7)	0.0 (0.0 - 17.1)	<0.01
Physical Activity (Kcal/week)		795 (238 - 1832)	945 (294 - 2254)	945 (285 - 1993)	1150 (520 - 2213)	<0.01
BMI (kg/m^2)		27.2 (± 5.2)	27.1 (± 4.8)	27.1 (± 4.5)	27.1 (± 4.4)	0.03
Systolic Blood Pressure (mmHg)		135.9 (± 21.3)	136.6 (± 20.7	135.8 (± 20.1)	132.1 (± 18.7)	<0.01
Diastolic Blood Pressure (mmHg)		71.9 (± 11.7)	71.9 (± 14)	72.1 (± 10.3)	70.6 (± 9.9)	0.08
Non-HDL Cholesterol (mg/dL)		156.6 (± 41.2)	156.5 (± 38.9	155.9 (± 36.7)	160 (± 34.9)	0.20
HDL Cholesterol (mg/dL)		50.6 (± 14.4)	52.1 (± 15.4)	52.6 (± 14.4)	54.7 (± 14.6)	<0.01
CRP (mg/L)		3.2 (1.5 - 8.2)	3.1 (1.3 - 6.4)	2.9 (1.2 - 6.3)	2.1 (1.0 - 4.3)	<0.01
Cystatin-C (mg/L)		1.11 (0.96 - 1.30)	1.04 (0.93 - 1.21)	1.01 (0.91 - 1.15)	1.00 (0.89, 1.12)	<0.01
Depressive Symptoms Score		5.8 (± 4.6)	6.1 (± 5.2)	4.9 (± 4.5)	4.2 (± 4.1)	<0.01
Frailty Score		4.3 (± 2.1)	3.9 (± 1.9)	3.6 (± 2.1)	3 (± 1.8)	<0.01

Diabetes					<0.01
	Normal	318 (63.1%)	246 (69.1%)	390 (74.3%)	574 (82.4%)	
	Impaired Fasting Glucose	64 (12.7%)	42 (11.8%)	61 (11.6%)	67 (9.6%)	
	Diabetes	122 (24.2%)	68 (19.1%)	74 (14.1%)	56 (8.0%)	
Aspirin Use		243 (48.2%)	172 (48.3%)	255 (48.6%)	272 (39%)	<0.01
Lipid Lowering Medication Use		42 (8.3%)	38 (10.7%)	44 (8.4%)	78 (11.2%)	0.23
Prevalent CVD		211 (41.9%)	115 (32.3%)	136 (25.9%)	101 (14.5%)	<0.01
Incident CVD rate (per 1,000 person years)*		121 (102, 142)	80 (68, 93)	59 (52, 67)	32 (28, 36)	<0.01

***** In participants without a prevalent cardiovascular disease at baseline

GED = General education development; BMI = body mass index, HDL = high density lipoprotein, CRP = C-reactive protein, CVD = cardiovascular disease

Table 2: Characteristics of participants with a high burden of subclinical vascular disease (index score ≥4), stratified by survival to < and ≥ 85 years of age)

	Age <85, index score ≥4 (N = 233)	Age ≥85, index score ≥4 (N = 128)	
	Mean (± SD) or Median (IQR) or N (%)		p-value
Age (years)	72.9 (± 1.4)	73.0 (± 1.5)	0.39
Male	144 (61.8%)	62 (48.4%)	0.02
Black	47 (20.2%)	26 (20.3%)	0.92
Less than High School Education	84 (36.1%)	32 (25%)	0.12
No Alcohol Consumption	137 (58.8%)	69 (53.9%)	0.57
Never Smoker	56 (24.0%)	49 (38.3%)	0.01
Years Quit (Among Former Smokers)	19.0 (± 13.2)	21.9 (± 13.8)	0.20
Pack Years	25.5 (0.0 - 49.7)	13.2 (0.0 - 36.5)	<0.01
BMI (kg/m^2)	27.7 (± 5.2)	27.7 (± 5)	0.96
Physical Activity (Kcal/week)	610 (158 - 1733)	630 (266 - 2010)	0.25
Systolic Blood Pressure (mmHg)	141.2 (± 23.3)	139.1 (± 22.1	0.38

Diastolic Blood Pressure (mmHg)	71.9 (± 11.6)	71.8 (± 11.4)	0.95
Non-HDL Cholesterol (mg/dL)	161.8 (± 42.8)	169.1 (± 38.1)	0.10
HDL Cholesterol (mg/dL)	47.8 (± 14.4)	49.7 (± 13)	0.21
CRP (mg/L)	4.2 (2.2 - 9.4)	2.9 (1.4 - 6.5)	0.01
Cystatin-C (mg/L)	1.16 (0.99 - 1.39)	1.07 (0.93 - 1.19)	<0.01
Depressive Symptoms score	6.2 (± 5)	4.7 (± 4.2)	0.003
Frailty score	4.6 (± 2)	3.8 (± 2)	<0.01
Diabetes	82 (35.2%)	21 (16.4%)	0.001
Aspirin Use	124 (53.2%)	62 (48.4%)	0.45
Lipid Lowering Medication Use	30 (12.9%)	23 (18%)	0.25
Prevalent CVD	139 (59.7%)	51 (39.8%)	<0.01
Incident CVD rate (per 1,000 person years)*	166 (131, 211)	64 (49, 84)	<0.01

***** In participants without a prevalent CVD at baseline

BMI = body mass index, HDL = high density lipoprotein, CRP = C-reactive protein, CVD = cardiovascular disease

Table 3: The association of subclinical vascular disease score with longer survival (≤80, 81-84, 85-89, and 90+ years)

	Demographic-Adjusted[a]			Adjusted[b]		
	N	OR[c] (95% CI)	p-value	N	OR[c] (95% CI)	p-value
All Participants						
Subclinical Vascular Disease[d]	2,082	1.35 (1.27, 1.44)	<0.01	1,912	1.22 (1.14, 1.31)	<0.01
Subclinical Vascular Disease, adjusted for intermediate CVD[d]	2,082	1.35 (1.27, 1.44)	<0.01	1,912	1.22 (1.14, 1.31)	<0.01
Participants Free of CVD at Baseline						
Subclinical Vascular Disease[d]	1,519	1.34 (1.25, 1.45)	<0.01	1,407	1.21 (1.12, 1.32)	<0.01
Subclinical Vascular Disease, adjusted for intermediate CVD[d]	1,519	1.34 (1.24, 1.45)	<0.01	1,407	1.22 (1.12, 1.32)	<0.01

[a]Model included clinical CVD status at baseline, age, sex, and race

[b]Model additionally included education, alcohol consumption, number of alcoholic drinks in the last week, diabetes status, smoking status, pack-years, BMI, physical activity, systolic blood pressure, diastolic blood pressure, HDL cholesterol, total cholesterol, depressive symptoms, frailty score, cystatin-C, CRP, and aspirin and lipid lowering medications

[c]Longer survival to ≥90 years versus <90 years, ≥85 years versus <85 years, or ≥81 years versus <81 years

[d]Modeled per one point lower SVD index score

CVD = cardiovascular disease, BMI = body mass index, HDL = high density lipoprotein, CRP = C-reactive protein, SVD = subclinical vascular disease

FIGURE LEGENDS:

Figure 1: Proportion of participants by survival group and subclinical vascular disease (SVD) score and clinical cardiovascular disease status. The proportion of participants surviving to different survival group among each disease group, and the proportion of participants with different levels of disease among each survival group were statistically significantly different (all comparisons $p<0.01$).

Figure 2: Cardiovascular disease incidence rate by survival group and subclinical vascular disease (SVD) score in participants without cardiovascular disease at baseline. The incidence rates in the different survival groups differed among persons among each disease group ($p<0.01$ for all), and the incidence rates also varied by subclinical disease status among each survival group ($p<0.01$ for ≤80, 81-84, 85-89; and $p=0.06$ for 90+)

Figure 1. Proportion of participants by survival group and subclinical vascular disease and clinical cardiovascular disease status

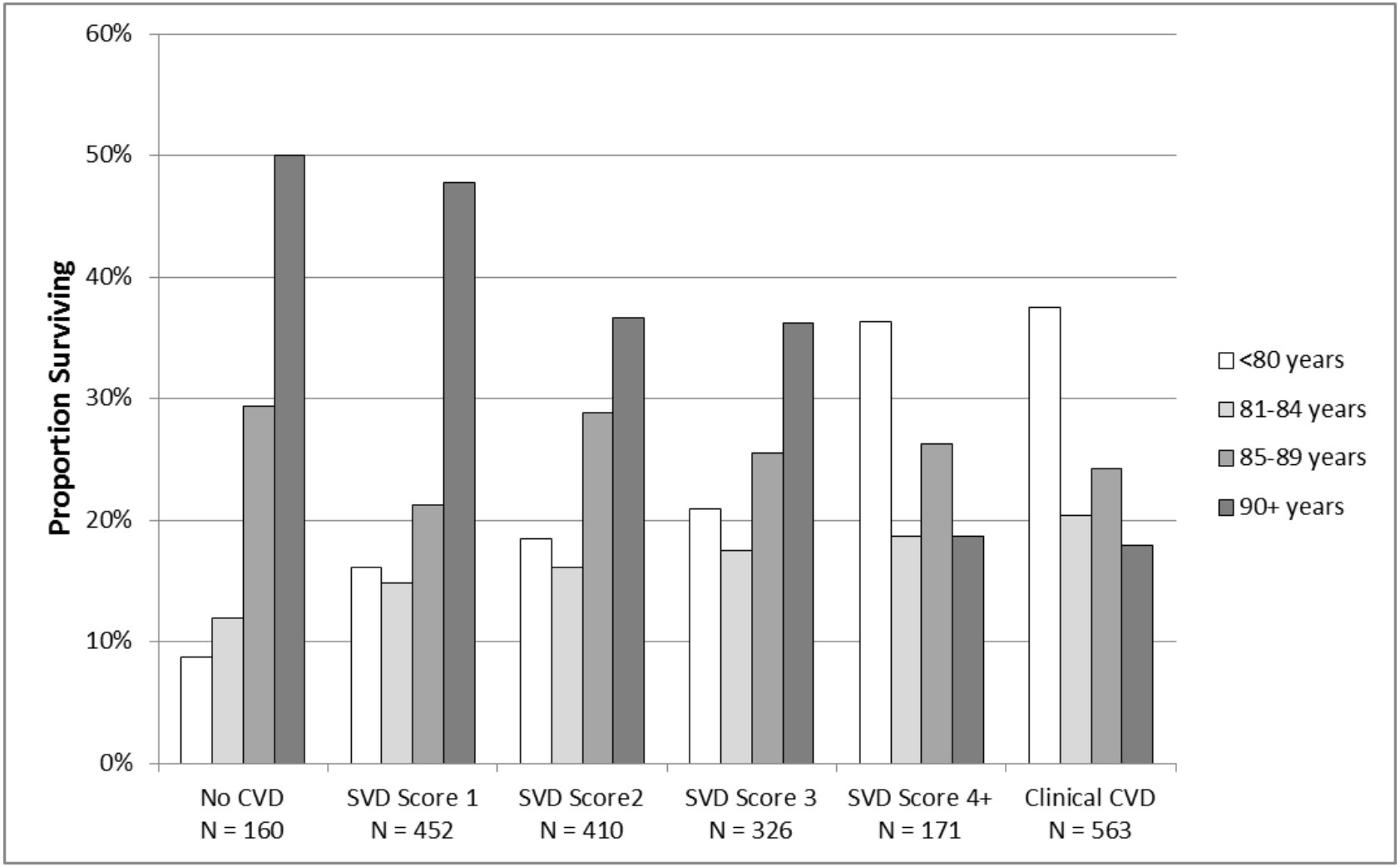

Figure 2. Cardiovascular disease incidence rate by survival group and subclinical disease status, in participants without cardiovascular disease at baseline