"Successful Aging"

Effect of Subclinical Cardiovascular Disease

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Background: Cardiovascular diseases are the primary cause of death in older adults. Among those without clinical disease, high levels of subclinical disease are associated with poor survival. The effect of the extent of subclinical cardiovascular disease on the quality of the remaining years has not been defined.

Methods: In a longitudinal cohort study, 2932 men and women aged 65 years and older were followed up for 8 years to determine the likelihood of maintaining intact health and functioning. *Successful aging* was defined as remaining free of cardiovascular disease, cancer, and chronic obstructive pulmonary disease and with intact physical and cognitive functioning.

Results: Younger age at study entry and a lower extent of subclinical cardiovascular disease were independently associated with the likelihood of maintaining successful aging. In age-stratified summaries, those with subclinical disease had a trajectory of decline similar to subjects 5 years older without subclinical vascular disease. Regression analyses showed that the decline associated with subclinical disease was equivalent to 6.5 (95% confidence interval, 6.4-6.6) years of aging for women and 5.6 (95% confidence interval, 5.4-5.8) years of aging for men. Individual measures of the extent of cardiovascular disease, diabetes mellitus, smoking, and higher C-reactive protein level were also independently predictive of fewer years of successful aging, but none of these factors substantially attenuated the effect of age itself.

Conclusions: There is a graded relationship between the extent of vascular disease measured noninvasively and the likelihood of maintaining intact health and function. Prevention of subclinical vascular disease may increase the quality and the quantity of years in late life.

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A man is as old as his arteries.
Attributed to Thomas Sydenham, as quoted by F. H. Garrison in the *Bulletin of the New York Academy of Medicine.* 1928;4:993

CARDIOVASCULAR DISEASES are the primary cause of death in older adults, and among those without clinical disease, high levels of subclinical disease are associated with poor survival.[1] The effect of the extent of vascular disease on the quality of the remaining years has not been defined. Studies of "healthy aging" or "successful aging" show that those who survive with intact health or function have low levels of modifiable risk factors for common chronic diseases, particularly risk factors for cardiovascular disease.[2-5] Risk factor modification can prevent cardiovascular events and mortality in older adults, but the effect of cardiovascular disease prevention on active life expectancy or successful aging is still uncertain. It is possible that cardiovascular disease prevention would have limited effects on a reduction of disability, because nonfatal yet prevalent conditions are also disabling in old age.[6]

Recent studies[7,8] of subclinical cardiovascular disease suggest that some measures of the extent of vascular disease are associated with adverse health effects even in those with no symptoms of vascular disease or history of myocardial infarction, stroke, or other vascular events. For example, those with subclinical peripheral arterial disease have mobility impairment even without claudication,[9] those with white matter changes on brain magnetic resonance imaging but no history of stroke have demonstrably lower levels of physical performance,[10] and those with subclinical disease appear to be more frail.[11] These data suggest that subclinical cardiovascular disease has adverse effects on health and function and, in addition to causing morbidity from heart disease directly, may contribute to disability and cognitive impairment. If true, then levels of subclinical vascular disease might predict not only better survival but also lower rates of physical and cognitive decline.

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In the present study, we defined criteria for successful aging, based on the conceptual framework of reaching old age without having experienced serious chronic illness and having maintained high levels of physical and cognitive functioning.[3,4] Successful aging is of interest because it is common in those with extreme longevity and may be in part genetically determined.[12] We hypothesized that there would be a graded relationship between the extent of cardiovascular disease measured noninvasively and the likelihood of maintaining successful aging. Such information would provide evidence as to whether noninvasive assessment of vascular disease might identify those most likely to age well or to benefit from cardiovascular disease risk reduction programs.

METHODS

POPULATION

The Cardiovascular Health Study (CHS) is an observational study of 5888 community-dwelling older adults, including 5201 participants recruited in 1989-1990[13] and 687 minority participants recruited in 1992-1993. Participants were recruited from a random sample of the Health Care Finance Administration Medicare eligibility lists in 4 US communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh (Allegheny County), Pa. Potential participants were excluded if they were institutionalized, wheelchair-bound in the home, or currently under treatment for cancer. All participants gave informed consent, and the institutional review board of each participating university approved the protocol.

The baseline examination (1989-1990 for the original cohort and 1992-1993 for the added minority cohort) assessed health history, health behaviors, cardiovascular risk factors, and measures of subclinical cardiovascular disease. Subsequent annual examinations included assessment of physical and cognitive functioning with periodic reassessment of medical history, including clinical and subclinical cardiovascular disease. Interim telephone and clinic contacts at 6 months were used to assess all hospitalizations and outpatient cardiovascular diagnoses.

CRITERIA FOR SUCCESSFUL AGING

We conceptualized *successful aging* as remaining free of major, life-threatening chronic disease and having normal physical and cognitive functioning, based on other definitions of successful aging.[3,4] Specifically, we operationalized the definition of successful aging at baseline to include those with no prior diagnosis of cancer, an absence of cardiovascular disease (CVD) (angina, myocardial infarction, cardiac revascularization procedure, congestive heart failure, stroke, transient ischemic attack, or claudication),[14] no chronic obstructive pulmonary disease (chronic bronchitis, emphysema, or asthma), no reported difficulty with any activities of daily living (ADL), and a modified Mini-Mental State Examination score in the 80th percentile or higher.[15]

Maintenance of successful aging over time was defined as remaining free of incident cancer, CVD, chronic obstructive pulmonary disease,[5] or new and persistent physical disability or cognitive decline. Death without a prior health event, disability, or cognitive decline was censored as a neutral event. If CVD death was the first indication of CVD, the participant was not considered to have incident CVD. Incident CVD hospitalizations were reviewed by an adjudication committee to confirm the hospital diagnosis. Hospitalization for cancer included any *International Classification of Diseases, Ninth Revision (ICD-9)* discharge code identifying cancer other than nonmelanotic skin cancer. Chronic obstructive pulmonary disease was assessed using hospital discharge codes 491, 492, and 493 for bronchitis, emphysema, and asthma, respectively. Annual telephone or clinic interviews were used to determine self-reported difficulty with 1 or more ADL or whether results on a clinic-administered cognitive function test indicated cognitive impairment. *Persistent ADL difficulty* was defined as self-report of difficulty with any ADL on 2 consecutive clinic visits or a single self-report of difficulty in a participant who subsequently died or was missing these data in all future years. Similarly, *cognitive decline* was defined as a score lower than 80 on the 100-point modified Mini-Mental State Examination on 2 consecutive visits, or lower than 80 on a single visit followed by no modified Mini-Mental State Examination score data in future years. *Consecutive visits* were defined as 2 visits with data, so that if a participant had data in years 6 and 8 and was missing data for year 7, then years 6 and 8 would be considered consecutive for that participant. The *date of decline* was defined as the first of the 2 consecutive visits recording decline, to allow inclusion of participants who had no subsequent visits following a decline. Data were available through June 30, 1998, for hospitalizations and through June 30, 1999, for clinic visits, thus allowing for ascertainment of cognitive or physical impairment through June 30, 1998.

NONINVASIVE ASSESSMENT OF CVD

We first examined a composite measure of several noninvasive measures of the extent of CVD[8] and then individual measures, including carotid ultrasonogram,[16] ankle-arm index (AAI),[17] and electrocardiogram[18] findings. Carotid stenosis greater than 25% was assessed by Doppler flow ultrasonography, and maximal near and far wall thickness was averaged for the internal and common carotid arteries. Quintiles of the combined internal and common carotid arteries were also examined, as this has been shown to be most predictive of CVD outcomes.[7] Ankle-arm index was examined at 0.1 increments below 1.1.[17] *Major ECG abnormalities* included 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.[19] The *composite measure of any subclinical disease* was defined as presence of any of the following: common or internal carotid wall thickness above the 80th percentile of the distribution for all CHS participants at baseline, maximum percent stenosis of the internal carotid artery greater than 25%, AAI of 0.9 or less, any major ECG abnormality, or Rose questionnaire findings that were positive for angina or claudication.

OTHER RISK FACTORS

To determine the independence of the associations of vascular measures with successful aging, other risk factors for disease, disability, and cognitive impairment were examined. These included demographic factors of age, race, and education; comorbidities of depressive symptoms and arthritis; cardiovascular risk factors; and inflammatory markers.

Depressive symptoms were assessed with the modified Center for Epidemiological Studies–Depression questionnaire,[20] and arthritis, smoking, and physical activity (expressed as energy expenditure) were assessed by self-report. *Hypertension* was defined as definite if reported and the patient was on appropriate drug treatment or if measured blood pressure was higher than 160/95 mm Hg, and as borderline if blood pressure was be-

tween 140/90 and 160/95 mm Hg. *Diabetes mellitus* was defined as known if reported and the patient was on appropriate medication, as new if measured fasting glucose was at least 126 mg/dL (7.0 mmol/L), and as impaired if fasting glucose was 110 or greater but less than 126 mg/dL (6.1-7.0 mmol/L). Body mass index was calculated as weight in kilograms divided by the square of height in meters. Systolic and diastolic blood pressure was measured according to a standard protocol. Blood was collected and analyzed in specimens collected at the baseline examination according to laboratory methods described previously[21] and included measurement of serum creatinine, fasting glucose and insulin, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, C-reactive protein (CRP), and fibrinogen.[22]

STATISTICAL ANALYSIS

Distributions of baseline characteristics were described for men and women, using means and SDs or proportions. Nonnormally distributed variables were summarized by their medians or geometric means. The proportions remaining successful at levels of selected risk factors, adjusted for age and cohort, were estimated by logistic regression. Life tables were generated by sex, age group, and subclinical disease status to determine the cumulative proportion remaining free of disease or disability in each stratum. This proportion provides an estimate of the probability that a person with the given characteristics will age successfully throughout the maximum follow-up of 9 years.

Multivariable analyses were done using accelerated failure time models[23] to determine which characteristics were predictive of remaining successful. The accelerated failure time model assumes that risk factors act to shorten or lengthen the time of remaining successful, such that the likelihood that an individual with a given risk factor remains successful until time t is equal to the likelihood that someone without the risk factor remains successful until time kt, where k is the acceleration factor. If k is greater than 1, the individual without the risk factor remains successful longer, and the person with the risk factor is said to have an accelerated failure time. If k is less than 1, the "risk" factor is beneficial to maintaining success, and if k is equivalent to 1, there is no difference in successful survival time between persons with and without the risk factor. The inverse of the acceleration factor k, provides an estimate of the proportion of years remaining successful in those with the given risk factor compared with those without. All models were adjusted for age, race, body mass index, years of education, depression score, and arthritis. Additional risk factors were allowed to enter in stages, with smoking, alcohol use, energy expenditure from physical activity, history of hypertension or diabetes mellitus, and blood pressure considered at stage 1. Once significant stage 1 variables were entered, the blood laboratory measurements were considered. In the final stage, measures of subclinical CVD were evaluated for entry. Skewed variables were log-transformed and tested linearly; results are presented in quintiles or clinical cutpoints to examine potential threshold effects. Multivariable models were generated separately for men and women, and sex interactions were tested for significance in a model including men and women. No significant interactions were found, and results of the stratified models were similar. We retained the model including men and women to estimate median years of successful life with the same set of predictors for both sexes. The median number of successful years was calculated from the final model for an idealized low-risk individual who had the best profile on each risk factor and an idealized high-risk individual who had the worst profile on each risk factor, for a selected age group and sex. The adjustment variables of years of education, body mass index, depression score, arthritis, and race were set to their mean values for the participants who were successful at baseline. Observed median survival was calculated from a life table.

To determine whether subclinical vascular disease and CVD risk factors were associated with more years free of physical and cognitive disability when not combined with the incident CVD outcome, we modeled separately ADL difficulty and a combined physical and cognitive disability, using the predictors identified in the successful aging models, with and without adjustment for intervening CVD. These models were sex stratified. Analyses were done using SPSS version 10 (SPSS Inc, Chicago, Ill) and Stata version 7 (Stata Corporation, College Station, Tex) and are based on the CHS database updated through September 30, 2001.

RESULTS

Of the 5888 subjects in the CHS, 5875 (3385 women and 2490 men) had sufficient data at baseline to be classified according to our successful aging criteria, and 49.9% (n=2932) were considered to have successfully aged at study entry. Of the 2943 who did not meet the entry criteria, the number and percentage with events in each domain were as follows, with lack of success in multiple domains possible: CVD, 1513 (51.4%); cancer, 840 (28.5%); chronic obstructive pulmonary disease, 751 (25.5%); ADL difficulty, 476 (16.2%); and Modified Mini-Mental State Examination score below the 80th percentile, 464 (15.8%). Women were more likely to have successfully aged than men: 53.2% (n=1801) of women vs 45.4% (n=1131) of men ($P<.001$). Subjects who were successful were, on average, about 2 years younger than those who were not successful (71.9 vs 73.8 years).

Table 1 describes the characteristics of these 2932 men and women. Of note, there was a spectrum of risk factors and subclinical vascular disease in these individuals. In the women, 11.2% were diabetic, 40.5% were hypertensive, 12.4% were current smokers, 17.9% had major ECG abnormalities, and 40.0% had carotid stenosis greater than 25%. Similarly, the successful men had a prevalence of diabetes mellitus of 15.3%, 37.2% had hypertension, 11.1% were smokers, 24.3% had major ECG abnormalities, and 43.9% had carotid stenosis.

Of these individuals classified as successfully aged at enrollment, 48.0% (n=1408) remained successful through follow-up. **Table 2** summarizes the outcomes separately for men and women. Because more than 1 outcome was possible for an individual, the table shows the totals of all outcomes and the first outcome experienced. Women were more likely to develop ADL disability, while men were more likely to have incident CVD or cancer ($P<.001$).

The proportions remaining successful throughout the 8-year follow-up are presented by risk factor status, adjusted for age and cohort, in **Table 3**. In men and women, those with the youngest age at study entry and without diabetes mellitus, hypertension, or subclinical vascular disease had the highest proportions remaining successful. A smaller percentage of African Americans remained successful compared with whites, but the difference was smaller in magnitude than that of age or diabetes mellitus status and was not statistically significant.

To better illustrate the combined relationship of subclinical disease and age to successful aging, we plotted

Table 1. Characteristics of Study Sample*

Characteristic	Women (n = 1801)	Men (n = 1131)
Demographic		
Age, mean (SD), y	71.6 (5.1)	72.3 (5.2)
Age, group, y		
65-69	774 (43.0)	408 (36.1)
70-74	574 (31.9)	394 (34.8)
75-79	302 (16.8)	196 (17.3)
80-84	112 (6.2)	103 (9.1)
≥85	39 (2.2)	30 (2.7)
Black race	248 (13.8)	138 (12.2)
High school graduate	1371 (76.1)	866 (76.6)
Subclinical vascular disease		
Internal carotid wall thickness, mean (SD), mm	1.28 (.50)	1.45 (.56)
Carotid stenosis >25%	721 (40.0)	497 (43.9)
Ankle-arm index <0.9	148 (8.2)	103 (9.1)
Major ECG abnormality	322 (17.9)	275 (24.3)
Other comorbid factors		
Depression score ≥10	213 (11.8)	75 (6.6)
Arthritis	938 (52.1)	446 (39.4)
Smoking		
Never	1056 (58.6)	390 (34.5)
Former	519 (28.8)	614 (54.3)
Current	224 (12.4)	125 (11.1)
Pack-years smoked, ever smokers only (median)	21.0 (23.0)	30.0 (28.0)
Alcohol use, drinks/wk		
≤7	1636 (90.8)	896 (79.2)
>7-14	92 (5.1)	96 (8.5)
>14	69 (3.8)	134 (11.9)
Diabetes mellitus		
Normal	1361 (76.0)	783 (69.2)
IFG	227 (12.6)	171 (15.1)
New-onset diabetes	107 (5.9)	88 (7.8)
Diabetic	95 (5.3)	85 (7.5)
Hypertension		
Normal	781 (43.4)	534 (47.2)
Borderline	288 (16.0)	176 (15.6)
Definite	730 (40.5)	421 (37.2)
Body mass index, kg/m^2	26.6 (4.9)	26.5 (3.7)
Physical activity, energy expended (median)	1102 (2004)	1367 (2228)
Systolic blood pressure, mm Hg, mean (SD)	135.8 (21.9)	135.9 (21.5)
Diastolic blood pressure, mm Hg, mean (SD)	69.9 (10.8)	73.2 (11.5)
Creatinine, mg/dL†	0.89 (0.22)	1.17 (0.36)
C-reactive protein, mg/L†	1.86 (4.8)	1.65 (6.9)
Fasting glucose, mg/dL†	103.8 (29.5)	107.8 (30.3)
Insulin, μIU/mL†	12.8 (20.1)	13.1 (19.2)
Triglyceride, mg/dL†	124.3 (72.2)	122.6 (71.2)
Total cholesterol, mg/dL	222 (38)	198 (35)
HDL cholesterol, mg/dL	59.7 (15.6)	48.3 (12.5)
LDL cholesterol, mg/dL	135 (36)	123 (33)
Albumin, g/dL	3.99 (0.28)	4.03 (0.29)
Fibrinogen, mg/dL	322 (63)	313 (64)

Abbreviations: ECG, electrocardiogram; HDL, high-density lipoprotein; IFG, impaired fasting glucose; LDL, low-density lipoprotein.

SI conversion factors: To convert insulin to picomoles per liter, multiply by 6.945; to convert creatinine to micromoles per liter, multiply by 88.4; to convert glucose to millimoles per liter, multiply by 0.0555; to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert cholesterol to millimoles per liter, multiply by 0.0259.

*Data are given as number (percentage) unless otherwise indicated. Some percentages do not sum to 100 because of rounding. The total sample size varies because of missing data.

†Geometric mean (SD).

the probability of remaining successful according to the composite measure of subclinical disease within age and sex strata. The **Figure** shows the cumulative proportions surviving successfully for the composite outcome and for the individual outcomes of ADL disability and cognitive decline. They illustrate the pronounced effect of age at study entry and subclinical disease on the likelihood of successfully aging throughout the follow-up. Within each age group, the participants with subclinical disease generally had a probability of remaining successful that was more similar to participants 5 years older who had no subclinical disease than to their own-age peers free of subclinical disease. The pattern is similar for those with ADL disability and those with cognitive decline. The effect of subclinical vascular disease was seen to essentially shift the age-related decline to an age approximately 5 years younger. In separate regression models for men and women with age and presence of subclinical disease as predictors, the effect of subclinical disease was equivalent to 6.5 (95% confidence interval, 6.4-6.6) years of aging in women and 5.6 (95% confidence interval, 5.4-5.8) years in men.

Results of the multivariable model are presented in **Table 4**. In these models, we considered 3 of the components of the composite subclinical disease index in more detail. The proportion given for each risk factor level represents the relative proportion of successful years experienced by someone with the risk factor, compared with someone without the risk factor who had equal values for the remaining variables in the model. Age at baseline remained strongly associated with successful aging, with those 85 and older having only about one quarter the number of successful years as participants aged 65 to 69. Men had on average fewer successful years than women (89% of the number of healthy years for women). Success rates were not significantly different in whites compared with African Americans. As expected, participants who did not smoke, were more physically active, and who did not have diabetes mellitus had more years of successful aging. A current smoker who had smoked more than 40 pack-years had 63% (0.77×0.82) as many healthy years as someone who never smoked and who had the same values on the other risk factors, even though the smoker had successfully aged to at least age 65 to be classified as successful at the baseline examination.

After adjustment for lifestyle factors, the subclinical disease measures of AAI, carotid wall thickness, and major ECG abnormality remained significantly related to years of success, as did the level of CRP at baseline. Each 0.1-U increase in the AAI was associated with an increase of 5% in the number of successful years. The proportion of successful years for an m-unit higher level of AAI is computed as $(1.05)^m$. Therefore, a participant with an AAI of 1.0 would have an estimated 10% more successful years than a participant with an AAI of 0.8, since $1.05^2 = 1.10$, all other factors in the model being equal. This result can only be interpreted for values of AAI within the range of our data, approximately between 0.5 and 1.5. Each quintile of increased carotid wall thickness was associated with fewer years of successful aging, with participants in the highest quintile having 69% of the number of successful years as participants in the lowest

Table 2. Successfully Aging Participants With Selected Health Events During 8 Years*

Event	Any Disease or Difficulty		First Disease or Difficulty	
	Women (n = 1801)	Men (n = 1131)	Women (n = 1801)	Men (n = 1131)
Cognitive impairment†	242 (13.4)	172 (15.2)	152 (8.4)	119 (10.5)
Activities of daily living difficulty	409 (22.7)	189 (16.7)	269 (14.9)	102 (9.0)
Cardiovascular disease	413 (22.9)	340 (30.1)	302 (16.8)	257 (22.7)
Cancer	187 (10.4)	171 (15.1)	136 (7.6)	124 (11.0)
Chronic obstructive pulmonary disease	70 (3.9)	57 (5.0)	24 (1.3)	22 (1.9)
Any of the above	900 (50.0)	624 (55.2)	900 (50.0)	624 (55.2)

*Data are given as number (percentage). Multiple outcomes per person are possible.
†Score less than 80 on the Mini-Mental State Examination.

quintile. Major ECG abnormalities were associated with about 81% of the number of successful years, which is similar to the association of a value of CRP in the highest quintile compared with the lowest quintile.

The accelerated failure time model can be used to estimate the median number of successful years according to values of the risk factors in the model. We calculated the median number of successful years for men and women in 5 age groups and for the lowest and highest levels of the Table 4 risk factors and tabulated the results in **Table 5**. The proportions in Table 4 can be used to estimate the association of an individual risk factor with the number of successful years by multiplying the proportion associated with that risk factor by the mean number of years for someone in the low-risk category in Table 5. For example, a 72-year-old woman with lowest values of all the risk factors listed in Table 4 would be expected to have 14 years of successful aging. If she were in the highest quintile of carotid wall thickness and had low-risk values for all of the other factors, the number of years would be reduced to 0.69×14, or 9.7 years. The association of several factors would be multiplicative, as is the effect of changing more than 1 value for a continuous risk factor, such as AAI.

Finally, we examined whether the ability to maintain success was due to the increased risk of vascular events in those with subclinical vascular disease, by examining the relationship of subclinical markers and CVD risk factors to intact physical and cognitive function as the outcome, adjusting for interim CVD events. Women had more years free of physical or cognitive impairment if they were nonsmokers, did not have diabetes mellitus, exercised, and had minimal carotid wall thickness. Adjustment for intervening CVD reduced the significance of carotid wall thickness ($P = .07$), but other factors remained significantly associated with years of living free of disability. In men, low systolic blood pressure and higher AAI were associated with more years free of cognitive or physical disability, with or without adjustment for intervening CVD.

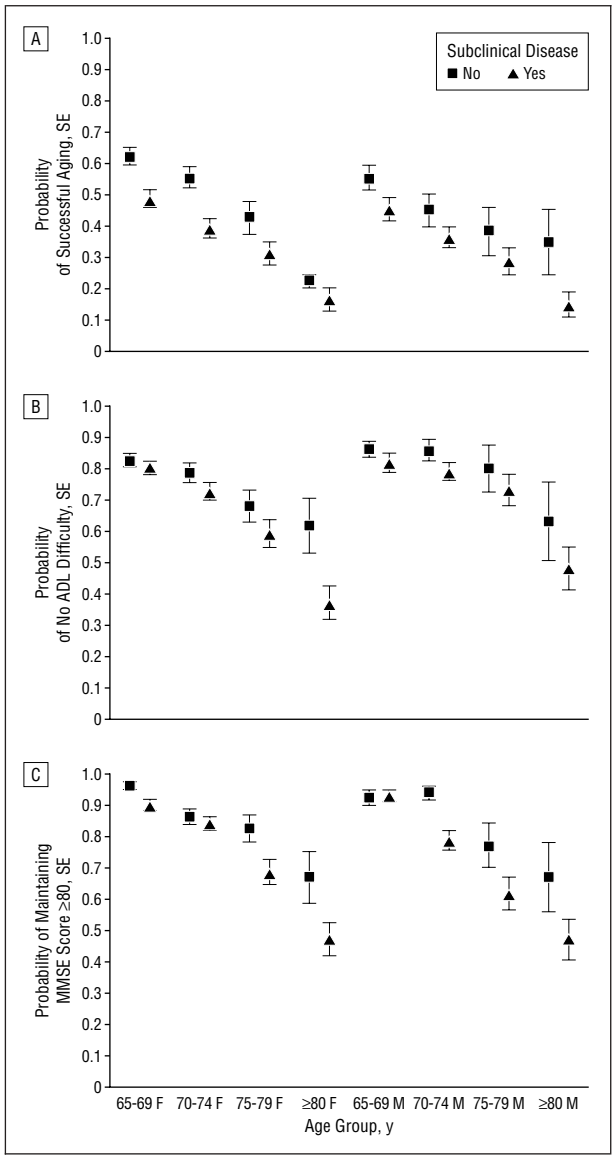
Table 3. Proportion of Men and Women With Successful Aging by Age, Subclinical Cardiovascular Disease (CVD), and Selected Risk Factors

Risk Factor	Women		Men	
	Adjusted %*	*P* Value†	Adjusted %*	*P* Value†
Age, y‡		<.001		<.001
65-69	59.1		53.8	
70-74	50.3	.001	44.8	.01
75-79	38.9	<.001	37.4	<.001
80-84	24.9	<.001	25.9	<.001
≥85	15.3	<.001	16.4	<.001
Race				
Nonblack	49.1	.07	45.2	.054
Black	38.7		29.3	
Subclinical CVD				
No	56.1	<.001	50.9	.002
Yes	42.9		40.9	
Diabetes mellitus		<.001		<.001
No	50.6		49.7	
Impaired fasting glucose	49.6	.80	33.9	<.001
New	37.9	.02	33.0	.004
Treated	25.7	<.001	32.7	.004
Hypertension		.003		.07
No	53.2		48.2	
Borderline	47.4	.11	41.3	.13
Yes	43.9	.001	41.1	.03

*Adjusted for age and cohort by setting age as 72 and cohort as 1 (original cohort) in a logistic regression.
†For 3 or more level categories, the first *P* value is for the overall measure; others compare each category to the first.
‡Adjusted for cohort only.

COMMENT

Men and women who reach old age in good health without disability or cognitive impairment vary widely in the likelihood of continuing to age successfully. The initial age at study entry was the strongest predictor of continued success, but even within age strata the number of expected years of success was strongly related to other factors, including the extent of subclinical vascular disease and health habits. Participants without subclinical vascular disease continued to successfully age approximately 5 to 6 years longer than those with subclinical disease (women, 6.5 vs men, 5.6 years). Those aged 80 to 84 with the lowest levels of vascular disease and no other risk factor could potentially have 7 to 8 years of continued success, on average. That the observed median number of successful years in this age group ranged from 3.8 to 4.3 suggests that most participants had 1 or more risk factors.



Probabilities of successful aging (A), no difficulty in activities of daily living (ADL) (B), and maintaining Mini-Mental State Examination (MMSE) score of 80 or higher (C), by sex, age group, and subclinical disease status. F indicates female; M, male. Bars indicate SEs.

Table 4. Proportion of Successful Years for Given Risk Factors Compared With Someone Without the Risk Factor, Multivariate Model (Mean Follow-up, 8 Years)

Risk Factor*	Proportion (95% Confidence Interval)	*P* Value
Age, y		<.001†
65-69	1.00 (Reference)	
70-74	0.85 (0.76-0.95)	.005
75-79	0.66 (0.58-0.75)	<.001
80-85	0.48 (0.40-0.57)	<.001
≥85	0.27 (0.21-0.36)	<.001
Male	0.89 (0.81-0.99)	.03
Black race	0.87 (0.71-1.08)	.22
Ankle-arm index, 0.1 U	1.05 (1.01-1.08)	.004
Combined carotid quintiles‡		<.001†
1	1.00 (Reference)	
2	0.90 (0.78-1.04)	.15
3	0.78 (0.67-0.90)	.001
4	0.77 (0.66-0.89)	.001
5	0.69 (0.59-0.80)	<.001
Major electrocardiogram abnormality	0.81 (0.73-0.90)	<.001
C-reactive protein, quintiles, mg/L		.02†
<0.74	1.00 (Reference)	
0.74-1.37	0.98 (0.85-1.13)	.78
1.38-2.20	0.98 (0.84-1.14)	.79
2.21-3.59	0.85 (0.74-0.99)	.04
≥3.60	0.82 (0.70-0.95)	.009
Current smoker	0.77 (0.65-0.90)	.001
Pack-years		.02†
None	1.00 (Reference)	
≤10	0.84 (0.73-0.98)	.02
>10-20	0.90 (0.76-1.07)	.23
>20-40	0.99 (0.85-1.15)	.91
>40	0.82 (0.71-0.95)	.01
Physical activity, kcal quintiles		.03†
Men/women		
<480/<320	1.00 (Reference)	
480-1069/320-824	1.12 (0.97-1.30)	.11
1070-1835/825-1440	1.19 (1.03-1.37)	.02
1836-3520/1441-2625	1.11 (0.96-1.28)	.16
>3520/>2625	1.27 (1.09-1.47)	.002
Diabetes mellitus		.004
None	1.00 (Reference)	
Impaired fasting glucose	0.94 (0.82-1.07)	.35
New-onset diabetes	0.78 (0.66-0.93)	.006
Known diabetes	0.77 (0.65-0.93)	.006

*Adjusted for body mass index, education, depression score, and arthritis in addition to the variables tabulated.

†Overall *P* values for carotid, C-reactive protein, age, pack-years, and physical activity are from a model with these terms modeled linearly.

‡Cutpoints combine internal and common carotid values, and the resulting values are not clinically meaningful.

Although the extent of established vascular disease was an important determinant of maintenance of success, it did not explain the association with age. Even the lowest-risk group older than 80 had a lower likelihood of successfully aging than younger individuals with subclinical vascular disease. Other factors, including diabetes mellitus and smoking, did not fully explain the association with age at study entry. Vascular disease is so strongly age-related that it has historically (see the introductory quotation by Sydenham)[24(p23)] and recently[25] been proposed as a biomarker of aging. These data might be interpreted to show that arterial disease accelerates important age-related declines, but do not entirely explain it. This observation is consistent with studies[26-28] showing that vascular disease is not an obligatory finding in all aged populations.

The independent associations of diabetes mellitus, smoking, and physical activity with fewer years of success is important because risk factors are modifiable. Furthermore, it suggests that their adverse effects on maintaining health and function may be mediated by pathways other than vascular disease. Previous work in this cohort has emphasized the importance of modifiable behavioral factors in preventing several important chronic diseases of old age.[5] A study in the Honolulu Heart Program cohort showed that smoking, diabetes mellitus, and hypertension are common factors underlying a composite outcome of successful aging that is similar to ours.[3] Smoking and physical activity were shown to dramatically affect active life expectancy in the MacArthur studies of successful aging as well.[29] The

Table 5. Estimated Median Years of Successful Life

	Women			Men		
Age, y	All Low Risk	All High Risk	Observed*	All Low Risk	All High Risk	Observed*
65-69	16.4	2.6	>9	14.7	2.4	8.9
70-74	14.0	2.2	8.1	12.5	2.0	7.4
75-79	10.8	1.7	6.3	9.7	1.5	4.8
80-84	7.8	1.3	4.3	7.0	1.1	3.8
≥85	4.5	0.7	1.9	4.0	0.6	2.3

*Median years of successful survival observed for each age group.

associations with the subclinical vascular disease markers shown herein illustrate the potential for successful aging that such interventions could achieve by a shift in the population to a lower degree of subclinical vascular disease. C-reactive protein level and increased physical activity were also associated with successful aging. Higher CRP levels have previously been documented to predict mortality,[30] CVD,[22] and CVD events[31] in older adults. Inflammation as measured by interleukin 6 has been shown to predict disability,[32] while associations with CRP are less consistent.[33] Factors that predict higher levels of disability include smoking and obesity, but the pathophysiologic basis of these associations is not well-defined. Additional work is needed to examine these factors,[34] as well as other factors such as insulin-like growth factor, sex steroid hormones, and homocysteine levels that are hypothesized to affect the aging process.[35]

There are increasing opportunities to identify genetic factors that might affect the age at onset of vascular disease.[36] There is also a growing recognition that there may be protective genetic factors that result in delayed onset of vascular disease, even in the presence of modifiable risk factors such as smoking and cholesterol.[37] Family history also continues to predict vascular disease in late life, and its role is being examined in longevity and successful aging.[38] Future studies should examine whether successful vascular aging is genetically determined, to what degree genetic predisposition is environmentally modified, and whether it is part of a general phenomenon of a slow rate of aging.

The participants of the CHS have been well characterized regarding vascular disease and disability over many years.[39] Non-CVD risk factors have been less completely characterized and may also be important. Another limitation of the study is that *ICD-9* codes for non-CVD conditions could have overestimated or underestimated their contribution to the outcome, which could bias associations of subclinical vascular disease with successful aging in either or both directions. It is noteworthy that fewer than one quarter of the cohort met the criteria for success at baseline and maintained health and function during 8 years. Although the use of the term "successful" to describe these individuals should not be interpreted to imply that most older adults are "failures," we simply retained conventional terminology as it is often used in the literature.

Finally, the potential for the extent of vascular disease to exert its effect on functioning in old age may well be due to its association with a higher rate of disabling cardiovascular events. These analyses suggest that the effects of CVD on functioning are subclinical in that the associations persisted even when disease was excluded from the outcome and intervening events were accounted for.

Improving the quality of late life and maintaining intact health and function are important public health goals. These data suggest that if we shift the burden of vascular disease to later in life, the age-related trajectory of decline should be attenuated by several years. Current treatments for cardiovascular risk factors, including smoking cessation, lipid lowering, blood pressure treatment, and avoidance of obesity through diet and exercise, are underutilized[40,41] but have been successful in preventing CVD events. Recent recommendations for risk factor modification suggest that markers of the extent of subclinical vascular disease may be useful to target intervention in older adults, especially those without elevations in cardiovascular risk factors.[42] These data suggest that, if these treatments shift the extent of subclinical disease to lower levels, the quality and the quantity of years should be improved. Prevention of CVD should be a major priority for the achievement of successful aging.

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