Midlife Risk Factors and Healthy Survival in Men

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Context Healthy survival has no clear phenotypic definition, and little is known about its attributes, particularly in men.

Objective To test whether midlife biological, lifestyle, and sociodemographic risk factors are associated with overall survival and exceptional survival (free of a set of major diseases and impairments).

Design, Setting, and Participants Prospective cohort study within the Honolulu Heart Program/Honolulu Asia Aging Study. A total of 5820 Japanese American middle-aged men (mean age, 54 [range, 45-68] years) free of morbidity and functional impairments were followed for up to 40 years (1965-2005) to assess overall and exceptional survival. Exceptional survival was defined as survival to a specified age (75, 80, 85, or 90 years) without incidence of 6 major chronic diseases and without physical and cognitive impairment.

Main Outcome Measure Overall survival and exceptional survival.

Results Of 5820 original participants, 2451 participants (42%) survived to age 85 years and 655 participants (11%) met the criteria for exceptional survival to age 85 years. High grip strength and avoidance of overweight, hyperglycemia, hypertension, smoking, and excessive alcohol consumption were associated with both overall and exceptional survival. In addition, high education and avoidance of hypertriglyceridemia were associated with exceptional survival, and lack of a marital partner was associated with mortality before age 85 years. Risk factor models based on cumulative risk factors (survival risk score) suggest that the probability of survival to oldest age is as high as 69% with no risk factors and as low as 22% with 6 or more risk factors. The probability of exceptional survival to age 85 years was 55% with no risk factors but decreased to 9% with 6 or more risk factors

Conclusion These data suggest that avoidance of certain risk factors in midlife is associated with the probability of a long and healthy life among men.

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THE WORLD'S POPULATION IS AGing. Persons alive at age 85 years or older, often designated the "oldest old," are the fastest-growing age group in most industrialized countries and are among the largest consumers of health care resources.[1] Identifying strategies for remaining healthy, vigorous, and disability-free at older ages has become a major priority, as reflected by the US Surgeon General's *Healthy People 2010* objectives,[2] the US National Institute on Aging Strategic Plan,[3] and increased study of healthy "successful"[4] or "effective"[5] aging.

In many ways, remarkable progress has been made in creating healthier seniors.[6] Seniors are living longer and with less morbidity and disability than in past years; however, health and survival benefits have been less apparent in men than in women.[7] Relatively few men actually live to oldest-old age. By age 85 years, women outnumber men by 2.2 to 1 in the United States.[8] This ratio exceeds 3 to 1 in nonagenarians and 4 to 1 in centenarians.[9] While the survival gap has narrowed recently in the United States,[8] some data suggest that healthier lifestyles in both men and women may further extend healthy years and narrow the gender gap.[10]

A challenge in research on aging and health is defining the phenotype. What is healthy aging and how do we measure it? A recent literature review identified more than 500 studies that examined some aspect of healthy aging,[11] but only 28 of these studies had operationalized definitions (using categorical or continuous variables) as an outcome measure. Fewer than half of these 28 were prospective studies. Prospective epidemiological studies with substantial numbers of long-lived participants and phenotypic information useful for gerontological research are rare but essential to shape definitions and identify risk fac-

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tors for health and survival at older ages.[11-13]

The Honolulu Heart Program/Honolulu Asia Aging Study (HHP/HAAS) has followed a cohort of US men of Japanese ancestry living in Hawaii for 40 years. The HHP/HAAS provides a valuable opportunity to define aging phenotypes and prospectively assess risk factors linked to healthy aging in men.[14] The HHP/HAAS participants have been well characterized in terms of functional status and incidence of chronic age-associated diseases, including cardiovascular disease and dementia.[15-18] These men provide an important window for understanding what is realistically possible for healthy aging in men.

For this study, we focused on a phenotype of healthy aging referred to by a recent National Institute on Aging expert panel as exceptional survival.[12] This phenotype is characterized by absence of morbidity and absence of physical/cognitive impairment in persons who survive to an advanced age. We focused on the age of 85 years to be consistent with the current definition of oldest old,[19] but since this choice is arbitrary, some of our analyses include survival to ages 75, 80, 85, and 90 years. We examined potential biological, lifestyle, and sociodemographic risk factors present at the baseline assessment in 1965-1968, when the study participants were middle-aged. Our goal was to identify risk factors for healthy survival that are easily measured in both clinical and research settings and may be modifiable for clinical, health policy, and epidemiological purposes.

METHODS

Study Population and Procedures

The HHP is a population-based, prospective study of cardiovascular disease among 8006 Japanese American men (recruited from 9877 men with valid contact information) who were born between 1900 and 1919 and lived on the island of Oahu in 1965.[15] The HAAS is an ongoing study of dementia in the HHP cohort that began in 1991.[17] The HHP cohort recruitment, design, and procedures have been described in detail elsewhere.[20,21] At the time of study enrollment (1965-1968), participants were aged 45 to 68 years (mean age, 54 years). Approximately 12% of these men were born in Japan and 88% were born in the United States. From the commencement of the HHP, information on the development of incident coronary heart disease and stroke, as well as mortality from all causes, has been obtained by monitoring obituaries in local newspapers (English and Japanese) and through surveillance of hospital discharge records.[15] A follow-up survey in the 1991-1993 examination found that only 5 men could not be traced for mortality information.[22]

For the purposes of this study, total mortality, physical function, cognitive function, and incidence of 6 major chronic diseases were assessed during 8 follow-up examinations, which were conducted through 2005. Of the 8006 original HHP/HAAS study participants, we excluded 1501 because they either died within 1 year of the study onset or had presence of clinical morbidity at the baseline examination based on self-reported history or clinical findings, which included coronary heart disease, stroke, cancer, diabetes, gastrectomy, chronic lung diseases, or kidney or liver diseases. An additional 685 participants who were missing information on physical function at baseline or follow-up examinations were excluded, leaving a total of 5820 participants in this analysis. Procedures were in accordance with institutional guidelines and approved by the Institutional Review Board of Kuakini Medical Center. Written informed consent was obtained from all study participants or family representatives if participants were unable to provide consent.

Risk Factor Measures

A physical examination was performed at baseline, which included height and weight, grip strength, seated blood pressure, and forced expiratory volume in the first second (FEV_1). Levels of total cholesterol, uric acid, glucose (1 hour after a 50-g glucose load), triglycerides, and hematocrit were determined from nonfasting blood samples. Routine urinalysis was also performed. A medical history including lifestyle factors such as smoking status, alcohol consumption, and physical activity[23] was obtained. Information was collected on sociodemographic characteristics including occupation.[24]

Outcome Measures

Initially, we classified participants into 1 of 4 phenotypes: (1) nonsurvivors—men who died before a specified age (75, 80, 85, or 90 years); (2) so-called "usual survivors but disabled"—men who survived until the specified age but with physical or cognitive disability and with or without a major chronic disease; (3) usual survivors with major chronic diseases but no disability; and (4) exceptional survivors—men who survived to the specified age without major chronic disease and also without cognitive or physical impairment. Since univariate analyses showed that the distributions of risk factors for the 2 usual survival phenotypes were very similar, these 2 groups were combined in the multivariate analysis.

Chronic diseases of interest in our analysis included coronary heart disease, stroke, cancer (excluding nonmelanoma skin cancer), chronic obstructive pulmonary disease, Parkinson disease, and treated diabetes. These 6 diseases were chosen on the basis of good phenotypic information in the HHP/HAAS cohort and the fact that they are among the most common age-associated chronic diseases. Presence of these diseases was identified by either the HHP/HAAS surveillance program or the HHP/HAAS follow-up examinations to the end of 2005. Screening for cognitive impairment was with the Cognitive Abilities Screening Instrument (score <74)[18] and diagnosed by cognitive function tests and clinical findings using standard Clinical Dementia Rating Scale criteria for all dementia

subtypes.[17] Physical impairment was defined as difficulty walking half-mile.

Statistical Analysis

Analysis of covariance was used to compare the baseline risk factors across the survival phenotypes adjusting for age at baseline. Odds ratios for mortality vs survival (for each specified age) and, among survivors, for having at least 1 morbid condition vs being free of these conditions were estimated using logistic regression models. For this analysis, continuous variables were dichotomized as high or low based on conventional cutoff points or median values.

A large number of variables were considered in the analysis. Backward stepwise logistic regression was used to select a subset of variables in the final model. This method starts with all variables in the model and reduces the model 1 variable at a time. This procedure continues until all variables in the model have *P* values smaller than the preselected level, such as .10.

All *P* values reported are for 2-tailed tests. A *P* value of .05 or less was considered statistically significant in univariate analyses and less than .10 was considered statistically significant in stepwise logistic regression. Including variables significant at the .10 level increased the size of the standard errors of the other regression coefficients somewhat but made comparison of the models for the 2 types of outcomes easier. Likelihood ratio tests were used to test for association between a set of independent variables and an outcome variable after adjusting for age. A difference of −2 log likelihood between a model with age plus other independent variables and that of a model with age only is asymptotically distributed as a χ^2 distribution.[25,26]

Our intention was to estimate the probability of overall survival or exceptional ("healthy") survival based on total number of risk factors. Risk scores based on simple numbers of risk factors are easily understood, can help guide clinical decision making, and may act as a motivator for both clinicians and patients. To assess cumulative effects of multiple risk factors on health outcomes, a survival risk score (SRS) was created. The risk factors used in our SRS were selected from variables significant in univariate analyses by backward stepwise logistic regression, deleting variables from the model that had $P>.10$.

Separate models were estimated for overall survival to age 85 years and exceptional survival at age 85 years as outcomes. Age at baseline was forced into all models. Overweight, hypertension, and high triglyceride level were defined using specific criteria from national expert panels.[27-29] Hematocrit and uric acid were dichotomized using the median value. High alcohol intake was dichotomized as 3 or more drinks/d (based on an increased risk of mortality in the HHP/HAAS cohort)[30] or less than 3 drinks/d. Smoking was dichotomized as ever or never. Education was dichotomized as high for achievement of graduation from high school or low otherwise.

Variables included in the SRS were overweight at midlife (body mass index ≥25; calculated as weight in kilograms divided by height in meters squared), low grip strength (<39 kg), hypertension (blood pressure ≥140/90 or prescription of an antihypertensive medication), hyperglycemia (≥200 mg/dL [11.1 mmol/L] 1 hour after glucose load), high triglyceride level (≥150 mg/dL [1.70 mmol/L]), high hematocrit (≥45%), high uric acid level (≥5.9 mg/dL), ever smoking, 3 or more alcohol drinks/d, low education (<12 years in school), and not married. The FEV_1 measure was significantly associated with outcome but was not included in the multivariate models because of invalid measurements for 20% of the participants.

The probability of exceptional survival and overall survival from age 55 years to age 75, 80, 85, or 90 years was computed using coefficients and standard errors estimated from multivariate logistic regression, adjusting for baseline age. Dummy variables were created to correspond to levels of SRS (0-5 and ≥6). The statistical software SAS, version 9 (SAS Institute Inc, Cary, NC) was used in the statistical analysis.

RESULTS

A total of 5820 individuals met the inclusion criteria for this study. Of these men, 3369 (58%) died before age 85 years and were classified as nonsurvivors. Seven hundred fifty-eight men with disease but no disability (13%) and 1038 men with disability without regard to disease status (18%) survived to age 85 years and were classified as usual survivors. The remaining 655 men (11%) survived to age 85 years without any of the 6 selected chronic diseases and without cognitive or physical impairment. These men were classified as exceptional survivors.

TABLE 1 displays the age-adjusted baseline characteristics of the 4 survival phenotypes: exceptional survivors, diseased usual survivors, disabled usual survivors, and nonsurvivors. The distributions of the risk factors were very similar in both usual survival groups. The *P* values for comparison of these 2 groups were greater than .05 for the vast majority of comparisons. Therefore, we combined these 2 groups to form a single group of usual survivors for multivariate analysis. Having redefined the survival groups as usual, exceptional, and nonsurvivors, we found marked differences across the groups for most risk factors.

Assessment of anthropometric and physiological variables revealed that exceptional survivors had stronger grip strength, suggesting increased physiological reserve and/or higher physical fitness at midlife. Exceptional survivors also tended to be leaner at both young (25 years) and middle (55 years) adulthood. Several hematological and biochemical measures were associated with exceptional survival, including lower levels of serum triglycerides, glucose, and uric acid, important markers of insulin sensitivity.[31]

Apart from age (and excluding FEV_1 because of its large number of missing values), there were 29 baseline variables in total from Table 1. To assess

whether the entire set of variables included variables that would be valid for later, more refined logistic regression analyses, we used likelihood ratio χ^2 tests for the entire set of 19 independent variables. After adjustment for age, the likelihood ratio χ^2 tests, when tested jointly in multiple logistic regression models, were $\chi^2_{19}=319.27$ ($P<.001$) for survival to age 85 years and $\chi^2_{19}=114.51$ ($P<.001$) for exceptional survival status (ie, survival to age 85 years free of the designated illnesses or disabilities). Therefore, there is extremely strong evidence that at least some of the original 19 independent variables were truly associated with our outcomes. Although each model as a whole was highly significant, it is obvious that many of the variables were not associated with the outcomes.

Table 1. Baseline Midlife Characteristics by Survival Phenotype (N = 5820)*

	Survival Phenotype				
Midlife (Baseline Examination) Characteristics	Exceptional (n = 655)	Usual, Diseased (n = 758)	Usual, Disabled (n = 1038)	Nonsurvival (n = 3369)	*P* Value for Trend
Anthropometric and physiologic					
Age at baseline, y*	55.5 (5.2)	55.0 (5.6)	51.7 (3.4)	54.1 (5.5)	
Height, cm	163.2 (5.4)	162.9 (5.6)	162.6 (5.6)	163.0 (5.7)	.23
Weight, kg	61.8 (7.8)	63.1 (8.0)	63.3 (8.8)	63.3 (9.8)	<.001
BMI in youth†‡	21.8 (1.9)	22.0 (2.0)	22.1 (2.1)	22.3 (2.3)	<.001
Overweight in youth (BMI ≥25), No. (%)‡	36 (5.4)	48 (6.4)	73 (7.5)	306 (9.6)	<.001
BMI in midlife†‡	23.4 (2.7)	23.9 (2.7)	24.1 (2.9)	24.0 (3.2)	<.001
Overweight in midlife (BMI ≥25), No. (%)‡	168 (26.6)	259 (34.8)	399 (37.1)	1216 (36.2)	<.001
Skinfold (triceps/subscapular), mm	23.2 (8.1)	24.4 (8.2)	24.8 (8.8)	24.7 (9.4)	<.001
Forced expiratory volume in 1 s, L	2.9 (0.4)	2.8 (0.5)	2.7 (0.4)	2.7 (0.5)	<.001
Grip strength, kg	39.5 (5.6)	39.2 (5.5)	38.8 (5.7)	38.5 (5.9)	<.001
Low grip strength (<39 kg), No. (%)	319 (44.3)	360 (44.4)	445 (49.3)	1719 (50.7)	<.001
Blood pressure, mm Hg					
Systolic	127.1 (17.6)	132.3 (17.9)	132.4 (18.9)	136.2 (21.3)	<.001
Diastolic	80.0 (10.5)	81.9 (10.8)	82.1 (11.2)	83.5 (12.0)	<.001
Hypertension, No. (%)§	185 (26.2)	302 (38.5)	371 (38.6)	1516 (44.8)	<.001
Hematological and biochemical					
Total cholesterol, mg/dL	216.0 (32.6)	222.9 (35.7)	218.1 (36.3)	218.3 (39.4)	.71
High total cholesterol (≥200 mg/dL), No. (%)	444 (68.8)	551 (73.5)	722 (69.0)	2308 (68.8)	.49
Triglycerides, mg/dL	208.2 (155.6)	236.8 (190.1)	230.9 (176.3)	249.7 (223.8)	<.001
High triglycerides (≥150 mg/dL), No. (%)	344 (56.8)	460 (63.5)	677 (66.2)	2178 (67.6)	<.001
Glucose, mg/dL‖	144.8 (42.0)	154.2 (48.5)	151.2 (43.6)	163.8 (56.8)	<.001
High glucose (≥200 mg/dL), No. (%)	69 (9.2)	126 (15.8)	130 (14.4)	725 (21.5)	<.001
Uric acid, mg/dL	5.78 (1.41)	5.90 (1.33)	6.03 (1.42)	6.11 (1.57)	<.001
High uric acid (≥5.9 mg/dL), No. (%)	285 (44.5)	375 (50.1)	545 (51.5)	1796 (53.5)	<.001
Hematocrit, %	44.3 (2.8)	44.7 (2.7)	44.6 (2.8)	44.9 (3.1)	<.001
High hematocrit (≥45%), No. (%)	295 (46.9)	417 (56.0)	555 (51.5)	1895 (56.7)	<.001
Health habits					
Ever smoker, No. (%)	364 (56.4)	469 (62.4)	663 (62.8)	2561 (76.1)	<.001
Smoking, pack-years	14.0 (19.6)	18.8 (22.4)	19.4 (22.0)	28.1 (25.5)	<.001
High alcohol consumption (≥3 drinks/d), No. (%)	42 (6.8)	76 (10.3)	123 (11.4)	592 (17.6)	<.001
Alcohol consumption, oz/mo	10.3 (16.3)	12.0 (20.9)	12.6 (24.8)	16.7 (26.9)	<.001
Physical activity index¶	32.8 (4.3)	32.6 (4.1)	33.4 (4.8)	32.9 (4.5)	.04
Sociodemographic, No. (%)					
Low education (<12 y)	279 (39.8)	380 (48.3)	513 (53.5)	1760 (52.0)	<.001
Unmarried	29 (4.3)	30 (3.9)	64 (6.3)	278 (8.3)	<.001
Blue collar occupation	362 (55.1)	441 (58.3)	693 (67.1)	2157 (64.1)	<.001

SI conversions: To convert total cholesterol, triglycerides, and glucose to mmol/L, multiply by 0.0259, 0.0113, and 0.0555, respectively.

*Data are expressed as mean (SD) unless otherwise indicated. All participants are Japanese American men followed from baseline (1965-1968) to the end of 2005; sample sizes may vary among presented variables because of missing values. All data are age-standardized to age 55 years. Exceptional survivors were those without disease or disability; nonsurvivors died before age 85 years; usual survivors with disease had no physical or cognitive disability; and usual survivors with disability were physically or cognitively disabled with or without disease.

†Youth is defined as age 25 years and midlife as ages 45 to 68 years.

‡Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

§Hypertension was defined as blood pressure of 140/90 or higher or antihypertensive medication use.

‖Nonfasting; 1 hour after 50-g glucose load.

¶Metabolic work performed in a typical 24-hour day.

TABLE 2 shows age-adjusted odds ratios for variables that were significantly associated with either usual or exceptional survival in the initial logistic regression analyses. Consistently high ORs for nonsurvival vs overall survival or usual survival vs exceptional survival were evident in overweight and lower-educated men. Marital status was associated with overall survival but not healthy survival.

Associations of particular variables with overall survival and exceptional survival are shown in TABLE 3, which displays the results of backward stepwise logistic regression that incorporated significant variables from the univariate analyses. It is evident that many common phenotypic measures are associated with both exceptional survival and overall survival. Higher ORs for usual survival vs exceptional survival were evident for all risk factors except marital status. A similar pattern, with the exception of education, was observed for nonsurvival. High blood glucose level, in particular, appears associated with both mortality and survival with morbidity or impairment. Interestingly, overweight at midlife is highly associated with exceptional survival but at best only moderately associated with overall survival; conversely, ever smoking is associated with overall survival but has only a borderline association with exceptional survival.

FIGURE 1 illustrates the estimated probabilities that a 55-year-old study participant who had no major disease at baseline would survive to ages 75, 80, 85, and 90 years according to cumulative risk factors from the baseline examination. The vertical lines are likelihood ratio–based 95% confidence intervals for the estimated probabilities. For all age outcome categories, the probability of survival declines approximately linearly as the number of risk factors increases. Among men with no risk factors at baseline, the estimated probabilities of surviving to ages 75, 80, 85, and 90 years are 0.89, 0.79, 0.69, and 0.33, respectively. The corresponding probabilities for men with 6 or more

Table 2. Age-Adjusted ORs of Selected Risk Factors for Death (Nonsurvival) or Unhealthy Survival (Usual Survival) at Age 85 Years (N = 5820)*

	Outcomes			
	Nonsurvival† vs Survival (n = 3369 vs 2451)		Usual Survival‡ vs Exceptional Survival§ (n = 1796 vs 655)	
Risk Factors	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Biological				
Overweight at midlife (BMI ≥25)‖	1.12 (1.01-1.25)	.04	1.67 (1.36-2.04)	<.001
Low grip strength (<39 kg)	1.21 (1.08-1.35)	<.001	1.13 (0.93-1.37)	.22
Hypertension (≥140/90 mm Hg or medication use)	1.50 (1.35-1.68)	<.001	1.84 (1.50-2.25)	<.001
High triglycerides (≥150 mg/dL)	1.23 (1.10-1.38)	<.001	1.41 (1.17-1.71)	<.001
High glucose (≥200 mg/dL)	1.78 (1.54-2.05)	<.001	1.70 (1.27-2.27)	<.001
High uric acid (≥5.9 mg/dL)	1.19 (1.07-1.32)	.001	1.32 (1.10-1.59)	.003
High hematocrit (≥45%)	1.23 (1.10-1.36)	<.001	1.33 (1.10-1.59)	.003
Lifestyle (health habits)				
Ever smoker	2.05 (1.83-2.29)	<.001	1.27 (1.06-1.53)	.01
High alcohol consumption (≥3 drinks/d)	1.97 (1.68-2.31)	<.001	1.84 (1.29-2.62)	<.001
Sociodemographic				
Low education (<12 y)	1.17 (1.05-1.30)	.003	1.62 (1.34-1.96)	<.001
Unmarried	1.70 (1.37-2.12)	<.001	1.25 (0.81-1.94)	.31

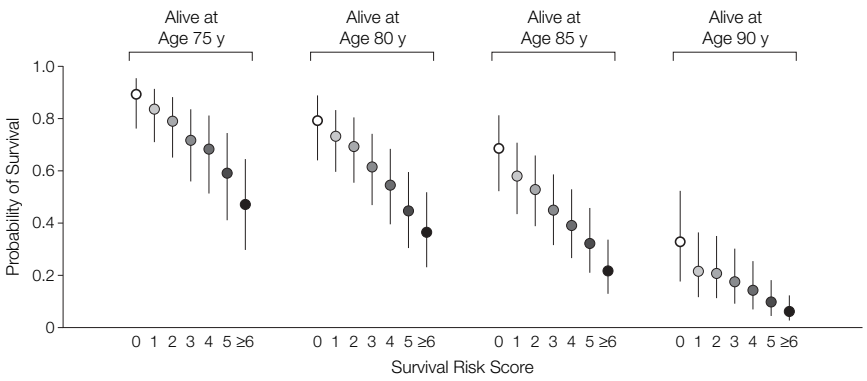
Abbreviations: CI, confidence interval; OR, odds ratio.
SI conversions: To convert triglycerides and glucose to mmol/L, multiply by 0.0113 and 0.0555, respectively.
*All participants were Japanese American men followed from baseline (1965-1968) to the end of 2005, sample sizes may vary among presented variables due to missing values; forced expiratory volume in 1 second was not included because of inappropriate measurement for 20% of the participants. Odds ratios greater than 1.00 indicate increased risk.
†Nonsurvivors died before age 85 years.
‡Usual survivors had 1 or more of 6 major chronic diseases and/or physical and/or cognitive disability.
§Exceptional survivors were very healthy men who survived free of 6 major chronic diseases and/or physical and/or cognitive disability.
‖Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Table 3. Stepwise Logistic Regression Model of Risk of Death (Nonsurvival) or Unhealthy Survival (Usual Survival) at Age 85 Years*

	Outcomes			
	Nonsurvival† vs Survival (n = 3198 vs 2327)‖		Usual Survival‡ vs Exceptional Survival§ (n = 1720 vs 607)‖	
Risk Factors	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Biological				
Overweight at midlife (BMI ≥25)¶	1.13 (1.00-1.28)	.044	1.49 (1.19-1.86)	<.001
High glucose (≥200 mg/dL)	1.64 (1.41-1.91)	<.001	1.65 (1.21-2.25)	.002
High triglycerides (≥150 mg/dL)	1.11 (0.99-1.25)	.08	1.26 (1.03-1.54)	.03
Hypertension (≥140/90 mm Hg or medication use)	1.45 (1.29-1.63)	<.001	1.61 (1.29-2.00)	<.001
Low grip strength (<39 kg)	1.25 (1.11-1.40)	<.001	1.24 (1.01-1.52)	.04
Lifestyle				
Ever smoker	1.94 (1.72-2.18)	<.001	1.23 (1.01-1.50)	.04
High alcohol consumption (≥3 drinks/d)	1.58 (1.34-1.88)	<.001	1.61 (1.11-2.34)	.01
Sociodemographic				
Low education (<12 y)			1.56 (1.28-1.91)	<.001
Unmarried	1.59 (1.27-2.00)	<.001		

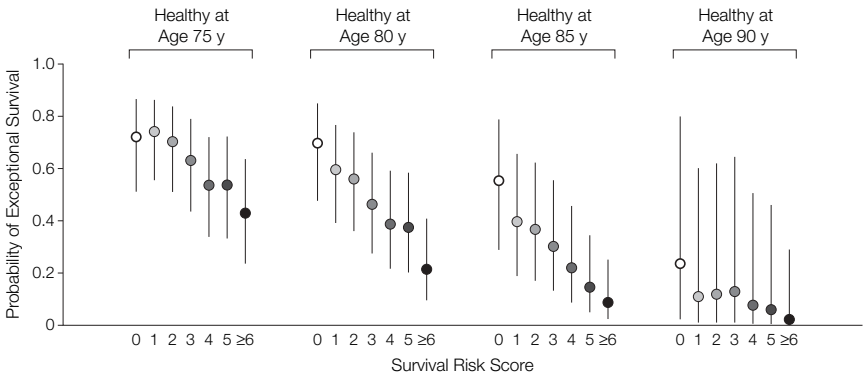
Abbreviations: CI, confidence interval; OR, odds ratio.
SI conversions: To convert triglycerides and glucose to mmol/L, multiply by 0.0113 and 0.0555, respectively.
*All participants were Japanese American men followed from baseline (1965-1968) to the end of 2005. Odds ratios greater than 1.00 indicate increased risk.
†Nonsurvivors died before age 85 years.
‡Usual survivors had 1 or more of 6 major chronic diseases and/or physical and/or cognitive disability.
§Exceptional survivors were very healthy men who survived free of 6 major chronic diseases and/or physical and/or cognitive disability.
‖The n is the sample size for the final stepwise logistic regression models, indicating variables not selected by the stepwise model for corresponding outcomes. Variables not selected by both stepwise logistic models included high uric acid and high hematocrit. Age was forced into the model (data not shown).
¶Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Figure 1. Probability of Survival by Age at Follow-up



All participants were Japanese American men followed from baseline (1965-1968) to the end of 2005. Survival risk score indicates number of risk factors (hyperglycemia, hypertension, high alcohol consumption, low education, overweight, high triglyceride level, low grip strength, ever smoker, and unmarried). Error bars indicate likelihood ratio–based 95% confidence intervals.

Figure 2. Probability of Exceptional Survival by Age at Follow-up



All participants were Japanese American men followed from baseline (1965-1968) to the end of 2005. Among those alive at a specified age, exceptional survival was defined as absence of 6 major chronic diseases and absence of physical and cognitive disability. Survival risk score indicates number of risk factors (hyperglycemia, hypertension, high alcohol consumption, low education, overweight, high triglyceride level, low grip strength, ever smoker, and unmarried). Error bars indicate likelikhood ratio–based 95% confidence intervals.

risk factors are 0.47, 0.37, 0.22, and 0.06, respectively.

FIGURE 2 shows the estimated probability of being free of the 6 major chronic diseases and major cognitive or physical impairment among survivors. Although the confidence intervals are wide, there is a fairly regular decline in the probability of being an exceptional survivor as the number of risk factors increases; the results for age 90 years are unclear because of the small number of men who were in such good health at age 90 years. Among men with no baseline risk factors, the estimated probabilities of being among the exceptional survivors at ages 75, 80, and 85 are 0.72, 0.70, and 0.55, respectively; the corresponding values for men with 6 or more risk factors are considerably lower at 0.43, 0.22, and 0.09.

The probability of being alive at a specified age and also being an exceptional survivor at that age, given that the participant was alive, is the product of the 2 individual probabilities; for 55-year-old men with no risk factors at baseline, the probabilities that they would be alive and free of the defined morbidities at ages 75, 80, and 85 are 0.64, 0.55, and 0.38, respectively. The corresponding probabilities for men with 6 or more risk factors are 0.20, 0.08, and 0.02.

COMMENT

Remaining healthy and functional at older ages is an increasingly important public health goal. Why is it that some men live to advanced age in good health? Is it only luck? We hypothesized that healthy survivors within the HHP/HAAS cohort would share similar risk factors in midlife. This study demonstrates that while chance and circumstance are applicable to everyone, there were major differences in risk factors for healthy survival among elderly men that were discernible 40 years prior. Several interesting patterns emerged from these data that appear consistent with recent theories of how aging occurs[32-34] and that also have important public health implications.

Anthropometric measures from this study, such as grip strength, suggest that it is important to be physically robust in midlife. This is consistent with theories of aging that suggest that better-built organisms last longer and that physiological reserve is an important determinant of survival.

Overall survival and exceptional survival were also more common among men with a lean body habitus in young and middle adulthood. This is a particularly relevant finding because there is increasing debate about whether or how much health risk is posed by overweight and obesity.[35-37] In addition, several risk factors that reflect insulin resistance were associated with overall survival and healthy survival in this population. This is consistent with previous findings regarding the mortality risks of insulin resistance and current hypotheses regarding insulin as a modifier of the aging process.[34,38-40]

Lifestyle factors have received increasing attention as modifiers of morbidity, but little is known about their potential impact on healthy survival.[41-44] Not surprisingly, smoking had

a major impact on overall survival and exceptional survival that was dose-dependent,[42] and overconsumption of alcohol was a significant risk factor for death[30] and for unhealthy survival. The most powerful sociodemographic attribute of exceptional survival was education. This is a recurring theme in studies of morbidity, in which higher-educated persons appear to fare better with regard to health outcomes than those less educated.[43] It would be interesting to study whether those who engaged in further education as adults (ie, "lifelong learners") fared better than those who did not with regard to health and survival at very old ages. Men who had a marital partner in midlife also survived longer but did not appear to be healthier in very old age.

Cumulative effects of common risk factors, several linked to insulin resistance, were associated with both overall survival and exceptional survival. The SRS, which combined risk factors selected in multivariate models, showed a high probability for both survival and exceptional survival with fewer midlife risk factors. In fact, there was near 60% probability for exceptional survival at oldest-old age (85 years) with no risk factors in midlife, and this number decreased to less than 10% with 6 or more risk factors. Only 11% of men actually met the criteria for exceptional survivorship at oldest-old age in our cohort, suggesting possible room for improvement in an already long-lived population.

This study has several limitations. Since our study population consists of ethnic Japanese men, there may be genetic, sociocultural, or other factors operative in this population that limits generalizability to other populations. There may also be cohort effects that favor particular outcomes in this group of men. In addition, since we excluded men with chronic diseases at baseline, there may be different aging trajectories for men who already possess comorbidities or disability in midlife, and factors associated with these comorbidities or disabilities may be less modifiable with age. In addition, since this study focused on men, the results may not be entirely applicable to women. Further comparisons between this study and other studies of healthy survival might be of interest.[14,44]

Strengths of the study include that it is among the largest, longest, and most complete follow-up studies on aging men. Our analyses were age-standardized to 55 years, which represents an age at which many men are facing significant midlife decisions about risk factor modification, including potential changes to physical activity, smoking, and other health habits. Therefore, information about the potential utility of such interventions for adding healthy years, rather than just additional years, could be highly motivating for men approaching retirement age. Disease incidence was determined by ongoing surveillance and participants were examined on multiple occasions, and since men with prevalent disease at baseline were excluded, this is a true incidence study. In this manner, we minimized potential effects of treatment for baseline diseases and changes in lifestyle on aging outcomes.

CONCLUSION

In summary, we have identified several potentially important risk factors for healthy survival in a large group of middle-aged men. These risk factors can be easily measured in clinical settings and are, for the most part, modifiable. This study suggests that common approaches that target multiple risk factors simultaneously, such as avoidance of smoking or hypertension, and approaches that enhance insulin sensitivity, such as maintaining a lean body weight, may improve the probability of better health at older ages. This may be especially important for men, few of whom survive to oldest-old age.

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