Exceptional Longevity in Men

Modifiable Factors Associated With Survival and Function to Age 90 Years

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Background: Prospective data on nongenetic determinants of exceptional longevity are limited, and information on long-lived men and their functional status is particularly sparse. We examined modifiable factors associated with a life span of 90 or more years and late-life function in men.

Methods: In this prospective cohort study of 2357 healthy men (mean age, 72 years) within the Physicians’ Health Study (1981-2006), biological and lifestyle factors and comorbid conditions were assessed by self-report with baseline and annual questionnaires. Mortality and incidence of major diseases were confirmed by medical record review. Late-life function was assessed 16 years after baseline by the Medical Outcomes Study 36-Item Short-Form Health Survey.

Results: A total of 970 men (41%) survived to at least age 90 years. Smoking was associated with increased risk of mortality before age 90 years (hazard ratio [HR], 2.10; 95% confidence interval [CI], 1.75-2.51), and similar associations were observed with diabetes (HR, 1.86; 95% CI, 1.52-2.26), obesity (HR, 1.44; 95% CI, 1.10-1.90), and hypertension (HR, 1.28; 95% CI, 1.15-1.43). Regular exercise was associated with a nearly 30% lower mortality risk (HR, 0.72; 95% CI, 0.62-0.83). The probability of a 90-year life span at age 70 years was 34% in the absence of smoking, diabetes, obesity, hypertension, or sedentary lifestyle. It ranged from 36% to 22% with 2 adverse factors and was negligible (4%) with 5. Compared with nonsurvivors, men with exceptional longevity had a healthier lifestyle (67% vs 33% had ≤1 adverse factor), had a lower incidence of chronic diseases, and were 3 to 5 years older at disease onset. They had better late-life physical function (mean ± SD score [maximum 100], 73 ± 23 vs 62 ± 30; P < .001) and mental well-being (mean score, 84 ± 14 vs 81 ± 17; P = .03). More than 68% (vs 45%) rated their late-life health as excellent or very good, and less than 8% (vs 22%) reported fair or poor health (P < .001 for trend). Regular exercise was associated with significantly better—and smoking and overweight with significantly worse—late-life physical function. Smoking also was associated with a significant decrement in mental function.

Conclusion: Modifiable healthy behaviors during early elderly years, including smoking abstinence, weight management, blood pressure control, and regular exercise, are associated not only with enhanced life span in men but also with good health and function during older age.

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Except for rare reports about long-lived men such as Sardinia’s “Methuselahs,”1 studies of exceptional longevity are dominated by data on women. It is unclear why relatively few men live to a very advanced age.

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Data from twin studies suggest that genetic determinants account for about 25% of the variation in life span,2 leaving perhaps 75% affected by potentially modifiable factors. However, modifiable factors that might interact with genetic influences to promote exceptional longevity have not been clearly identified. Prospective studies of mortality risks in elderly populations typically have had short observational periods of 5 to 10 years,3,4 with some exceptions,5,6 and have focused on survival within average life spans of 75 to 85 years.5,6 Studies of nonagenarians and centenarians, on the other hand, generally have been retrospective or cross-sectional analyses of relatively small numbers of survivors, including few men.9,10 In addition, prevalence of disease and disability in these oldest populations is typically high,11,12 and it is unclear what factors earlier in life might potentiate not only a very long life but also good health and function at an advanced age.

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Therefore, we used prospective data on more than 2350 men in the Physicians’ Health Study (PHS) who had the potential to live to or beyond age 90 years during a 25-year follow-up to address 2 principal questions. First, what potentially modifiable factors are associated with survival to an exceptional age in men (defined by us as \( \geq 90 \) years)? Second, do men with exceptional longevity have reduced incidence of age-associated diseases? We also assessed functional status in late life to determine if modifiable factors associated with longevity were also associated with good health and function at an advanced age.

**METHODS**

**STUDY POPULATION**

Participants were enrolled in the PHS, a cohort of 22,071 US male physicians assembled in 1981 to 1984 as a randomized trial of aspirin and beta carotene in the primary prevention of cardiovascular disease and cancer. Men were generally healthy at randomization, without a history of cancer (excluding non-melanoma skin cancer), myocardial infarction, transient cerebral ischemia or stroke, or other serious diseases. A detailed description of the PHS has been previously published. Each participant provided written consent, and the PHS was approved by the institutional review board of Brigham and Women’s Hospital, Boston, Massachusetts.

Participants in the present study were born on or before December 31, 1915, and had the potential to survive to age 90 years during follow-up ending March 31, 2006. We defined survival to age 90 as “exceptional longevity” because it far exceeded the 46- to 52-year estimated life expectancy for a man born in the United States in 1900 to 1915. Furthermore, men reaching age 90 years would have lived 10 to 15 years longer than the predicted remaining life expectancy for men in their birth cohort surviving to age 65 to 70 years.

**EXPOSURE INFORMATION**

**Baseline Data**

Participants gave self-reported information on demographic and health variables, including birth date, height, weight, systolic and diastolic blood pressures, history or treatment of hypertension (systolic/diastolic blood pressure \( \geq 140/\geq 90 \) mm Hg), total cholesterol level, history or treatment of high cholesterol level (\( \geq 240 \) mg/dL), history of diabetes or angina, smoking status (never, former, or current), frequency of alcohol consumption (rarely/never, 1-3 drinks per month, 1-6 drinks per week, or \( \geq 1 \) drink per day), and frequency of vigorous exercise sufficient to cause sweat (rarely/never, \(<1 \) time per week, 1-6 times per week, or \( \geq 1 \) times per day). Body mass index was calculated as weight in kilograms divided by height in meters squared.

**Follow-up Data**

Twice during the first year and annually thereafter, participants were sent questionnaires asking about changes in health or lifestyle habits, occurrence of chronic diseases or risks, and end points of interest. Nonrespondents were contacted by telephone. The percentage of participants with complete questionnaire data was greater than 96%.

**OUTCOMES**

**Mortality**

Survival to age 90 years was the primary outcome of this study. Deaths were confirmed by the PHS end points committee of physicians after review of medical records, autopsy reports, and death certificates. The follow-up rate for mortality in the PHS approximates 99%.

**Disease**

Secondary outcomes were major age-related diseases: cancer (excluding nonmelanoma skin cancer); coronary heart disease (myocardial infarction, coronary artery bypass graft, or percutaneous coronary angioplasty); and stroke. These outcomes were confirmed through medical record review by the PHS end points committee according to previously described procedures. We also examined occurrence of heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, Parkinson disease, and arthritis. Only the first event in each disease category was considered for analysis.

**Function**

We assessed functional status by the physical function and mental health subscales of the Medical Outcomes Study 36-Item Short-Form 36 Health Survey (SF-36) included in the 16-year follow-up questionnaire (1998-1999). Each subscale is scored separately from 0 (lowest level of functioning) to 100 (highest level). For this study we also scored separately 2 questions from the mental health items relating to depression. We used the SF-36 questionnaire on self-rated health as a general measure of health-related quality of life. We assessed social contact by questions relating to frequency of contact with a close confidant.

**STATISTICAL ANALYSES**

We compared survivors to age 90 years with nonsurvivors in baseline characteristics, follow-up data, and incidence of outcomes using \( \chi^2 \) tests for categorical variables and paired \( t \) tests or nonparametric tests, as appropriate, for continuous variables. We used Cox proportional hazards models to calculate the hazard ratio (HR) and 95% confidence interval (CI) for mortality before age 90 years according to baseline factors. Person-time was calculated from PHS enrollment to the minimum date of age 90 years, last contact, or death. All participants had the potential to reach age 90 years. We adjusted for baseline age (continuous) in an initial model and included adjustment for the following additional baseline factors in a multivariable model: body mass index; smoking status; alcohol intake; exercise frequency; history of hypertension, diabetes, high cholesterol level, or angina; and randomized treatment assignments (aspirin or beta carotene). Models including quadratic and cubic adjustments for baseline age did not improve model fit. Tests for linear trend across categorical variables were performed by entering the variable as a single ordinal term in the models. The assumption of proportional hazards was assessed by Schoenfeld residuals and was satisfied.

To illustrate the estimated probability of 90-year survival according to specific baseline risks and their additive effects, we used a logistic regression model with the same covariates and adjustments as in the multivariable proportional hazards model. In secondary analyses, we examined possible effect modification by birth cohort on survival to age 90 years through strati-
Of 2357 men with the potential to reach age 90 years during the 25-year follow-up study, 970 (41%) survived to or beyond age 90 years and 1387 did not (median follow-up: survivors, 17.9 years to age 90 years; nonsurvivors, 11.7 years). Mean ages at death were 83 years (nonsurvivors) and 93 years (518 survivors [53%] who died during continued observation) ($P<$ .001).

Table 1 gives the baseline characteristics of the population. The mean age was 72 years (range, 66-84 years), with survivors being slightly older. Survivors were less likely to be obese or have smoking history and were more likely to exercise than nonsurvivors. They had slightly lower blood pressures, and fewer had hypertension, diabetes, and angina. Prevalence of chronic disease was low in this population, and survivors and nonsurvivors showed little difference.

Table 2 gives age- and multivariable-adjusted HRs for mortality before age 90 years for potentially modifiable baseline factors. Current smoking was associated with a 2-fold increased risk of mortality (HR, 2.10; 95% CI, 1.75-2.51). Diabetes, obesity, and hypertension were associated with increased risks of 86%, 44%, and 28%, respectively. In contrast, vigorous exercise was associated with approximately 20% to 30% decreased mortality risk before age 90 years ($P$ value for trend, .003). Alcohol intake and high cholesterol level showed no mortality effects.

Incidence of cancer and cardiovascular disease, as well as associated risk factors, was lower among survivors compared with nonsurvivors and occurred at a 3- to 5-year older age. Similar patterns were apparent for other age-associated diseases (Table 3).

In age-stratified analyses, mean age at death was 9 years older for survivors to age 90 years who later died during the study period, compared with nonsurvivors, in both birth cohorts (1898-1907 and 1908-1915). Patterns of factors associated with 90-year survival were similar in the 2 cohorts, and there was no effect modification by birth year ($P$ value for interaction for all covariates, >.11). Increased risks of mortality before age 90 years were associated with smoking (103%-201%), diabetes (61%-92%), obesity (36%-44%), and hypertension (28%-38%). Regular exercise was associated with a 30% decreased mortality risk before age 90 years in both groups. There was no influence of birth cohort on incidence or age at onset of disease outcomes.

Compared with having no adverse baseline factors (smoking, diabetes, obesity, hypertension, or sedentary lifestyle), the age-adjusted odds of survival to age 90 years with 1, 2, 3, or 4 or more adverse factors was reduced by 33%, 49%, 75%, and 88%, respectively ($P$ value for trend, <.001). Survivors had significantly fewer adverse factors at baseline compared with nonsurvivors, including a significantly greater number with none (Table 4).

The Figure illustrates the association between specific factors at age 70 years and the probability that a man would live to age 90 years. If he did not smoke and had normal blood pressure and weight (BMI <25), no diabetes, and a moderate exercise habit (2-4 times per week),
his probability of living an additional 20 years was 54%. If he had a sedentary lifestyle, however, his probability was only 44%. If also hypertensive, obese, or a smoker, his probability of achieving a 90-year life span was reduced to 36%, 26%, and 22%, respectively. With 3 adverse factors (eg, sedentary lifestyle, obesity, and diabetes), his probability was only 14%, and it was negligible (4%) with 5 factors.

A sample of 686 men, mean age 86 years (range, 83-89 years), provided functional assessment approximately 16 years after baseline (506 survivors and 185 nonsurvivors). Survivors scored significantly higher in physical function and mental health, and they reported less depression than nonsurvivors (Table 5). They had better self-rated health (P value for trend, <.001), and more than 68% considered their health to be “very good” or “excellent” compared with less than 45% among nonsurvivors. A small group of survivors aged 90 to 101 years at assessment (n = 110) reported similar self-rated health, with 67% considering it to be “very good” or “excellent.” Survivors and nonsurvivors did not differ in social contact. Survivors had lower incidence and later age at onset of age-related diseases compared with nonsurvivors, similar to the pattern of the total study population (Table 3).

Modifiable behaviors associated with survival to exceptional age also showed a significant impact on function. Smoking or overweight was associated with substantially worse physical function score (up to 10.3 and 8.9 points lower, respectively) (Table 6). Moderate vigorous exercise, in contrast, was associated with significantly better physical function (up to 10.6 points higher score). Smoking also was associated with a significant dec-
In this 25-year prospective study of 2357 men, potentially modifiable biological and behavioral factors were associated with exceptional longevity of 90 or more years. Smoking, diabetes, obesity, and hypertension significantly reduced the likelihood of a 90-year life span, while regular vigorous exercise substantially improved it. Birth cohort did not influence these associations. Furthermore, men with a life span of 90 or more years also had better physical function, mental well-being, and self-perceived health in late life compared with men who died at a younger age. Adverse factors associated with reduced longevity—smoking, obesity, and sedentary lifestyle—also were significantly associated with poorer functional status in elderly years.

Men living to age 90 years or older had a lower incidence and older age at onset of cancer, coronary heart disease, stroke, and other diseases than did men dying at a younger age. These prospective findings support observations from cross-sectional and retrospective studies of nonagenarians and centenarians hypothesizing that exceptional longevity is achieved by escaping or delaying disease processes responsible for high morbidity and mortality. However, our results also extend these studies by demonstrating the strong association between non-genetic, highly modifiable biological and behavioral factors and exceptional life span that includes both reduced or delayed disease as well as good functional status at an advanced age.

Longitudinal studies of elderly cohorts have documented the unfavorable mortality risks of smoking, diabetes, obesity, hypertension, and physical inactivity, although prospective data on their risk to survival beyond 85 years have been limited. Our study demonstrates the significant and progressive reduction in the probability of an exceptional 90-year life span by the accumulation of adverse modifiable factors. Interestingly, men with exceptional longevity had healthy behaviors and few adverse factors and lived on average 10 years longer than men with less favorable characteristics. Although the impact of certain midlife mortality risks in elderly years is controversial, our study suggests that...
many remain important, at least among men. Not only were smoking, diabetes, obesity, hypertension, and physical inactivity negatively associated with exceptional longevity, but smoking, obesity, and inactivity were also strongly associated with poorer function at advanced age. Thus, our results suggest that healthy lifestyle and risk management should be continued in elderly years to reduce mortality and disability.

This study has a number of strengths, including prospective design, large sample size, substantial data on risk factors, completeness in ascertainment and number of outcome events, and long follow-up. This study also has several potential limitations. Information on biological and behavioral factors was self-reported, and inaccurate measurements and random misclassification were possible, which could underestimate associations. Restricting the population to initially healthy, mostly white, male physicians affects the generalizability of the results.
ity of results, although it reduces confounding by disease, education, socioeconomic status, and presumed access to health care. Furthermore, restriction to male subjects was an important advantage because existing data on exceptional longevity have come principally from women. Although we adjusted for many factors potentially associated with longevity, our analyses did not include a number of other variables that also may influence life span. Finally, this study did not capture the effect of possible changes in all risk factors and in functional status over the follow-up period.

In summary, these prospective data from 2357 men suggest that modifiable biological and lifestyle factors, assessed at a mean age of 72 years, are associated with exceptional longevity of 90 or more years and with high functional status in late life. If confirmed in other studies, this would suggest that encouraging favorable lifestyle behaviors, including smoking abstinence, weight management, blood pressure control, and exercise, may not only enhance life expectancy but may also reduce morbidity and functional decline in elderly years.

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