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Physical Activity, Cognitive Function, and Mortality in a US National Cohort

R.F. GILLUM, MD, MS and THOMAS O. OBISESAN, MD, MPH

Department of Medicine, Howard University College of Medicine, Washington, DC.

Abstract

PURPOSE—Increasing physical activity is postulated to slow cognitive decline associated with aging. Low levels of both physical activity and cognitive function are associated with increased risk of mortality. We test the hypothesis that the relative protective effect of high physical activity level as related to mortality is greater in persons with impaired cognitive function than in others.

METHODS—Data were analyzed from a longitudinal mortality follow-up study of 5903 American men and women aged 60 years and older examined in 1988 to 1994 who were followed an average of 8.5 years. Measurements at baseline included self-reported leisure-time physical activity (LTPA), a short index of cognitive function (SICF), sociodemographic data, health status, and physical and biochemical measurements.

RESULTS—Death during follow-up occurred in 2431 persons. In bivariate cross-sectional analyses, more frequent LTPA was associated with greater cognitive function. In proportional hazards regression analysis, no significant interaction of LTPA with cognitive function was found; however, there was a significant age-LTPA interaction. After adjusting for confounding by baseline sociodemographic data and health status at ages 60 to 74, the hazards ratio (95% confidence intervals) was for LTPA more than 8 times weekly compared with none (0.51; 0.38–0.76, p < .001) and for low SICF score compared with high 1.43 (1.36; 1.00–1.84, p < .05). After controlling for health behaviors, blood pressure, and body mass, C-reactive protein, and high-density lipoprotein cholesterol, the LTPA hazards ratio was 0.52 (0.35–0.78; p = .002), but cognitive function was no longer significant. At ages 75 and older, results were similar for LTPA, but cognitive function remained significant after adjustment.

CONCLUSIONS—In a nationwide cohort of older Americans, analyses demonstrated a lower risk of death independent of confounders among those with frequent LTPA. Much of the effect of low cognitive function could be explained by other risk factors at ages 60 to 74 but not 75 years and older.

Keywords

Aging; Cognitive Function; Dementia; Exercise; Mortality; Physical Activity

INTRODUCTION

Both sedentary lifestyle and impaired cognitive function are prevalent concomitants of aging in industrialized nations (1-3). Cognitive function has been found to be inversely associated

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Address correspondence to: Dr. R. F. Gillum c/o Dr. T. O. Obisesan, Howard University Hospital, 2041 Georgia Ave, Washington, DC 20060. Tel.: 202-865-3397; Fax: 202-865-3777. rfg2.howard.edu@gmail.com..

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with physical activity and subsequent mortality in elderly adults in a number of previous studies (4–7). Mechanisms remain obscure. Likewise, total, occupational, and leisure-time physical activity (LTPA) have been found to be inversely related to mortality from all causes, cardiovascular disease, and some cancers (8–12). Mechanisms may include improved fibrinolytic activity, hemostatic function, and glucose tolerance and reduced body fat, lipid profile, blood pressure, inflammation, and oxidative stress, leading to less atherosclerosis, as well as improved coping with stressful life events and reduced depression, leading to health-promoting physiological effects of decreased chronic sympathoadrenal activation improved immune function and less chronic inflammation (8, 13). However, findings regarding interactions and independence of cognitive function and physical activity of one another and possible interactions are lacking in studies of mortality.

We test the hypotheses of independent, inverse associations of LTPA and score on a test of cognitive function with mortality in older persons in the US population. We further test the hypothesis that the effect of cognitive function score is modified by LTPA, the effect being less among the most-active compared with the least-active persons. We analyzed newly available data from a national health examination survey-linked mortality file conducted with scientific sampling and state-of-the-art interviewing, examination, and laboratory methods.

MATERIALS AND METHODS

Subjects

The Third National Health and Nutrition Examination Survey (NHANES III) was conducted in 1988 to 1994 on a nationwide multistage probability sample of 39,695 persons from the civilian, noninstitutionalized population aged 2 months and older of the United States. Persons ages 60 and older, African Americans, and Mexican Americans were oversampled. Details of the plan, sampling, operation, response, and institutional review board approval have been published, as have procedures used to obtain informed consent and to maintain confidentiality of information obtained (14). The personal interviews and physical and laboratory examinations of NHANES III subjects provided the baseline data for the study.

This analysis was undertaken on the basis of the public-use version of the NHANES III linked-mortality file with mortality data through 2000 (15). Of 33,994 persons with baseline interview data, 13,944 were younger than 17 years of age, and 26 lacked data for matching, leaving 20,024 eligible for mortality follow-up. The NHANES III-linked mortality file contains information upon the basis of results from a probabilistic match between NHANES III and the National Center for Health Statistics National Death Index records. The NHANES III-linked mortality file provides mortality follow-up data from the date of NHANES III survey participation (1988 1994) through December 31, 2000.

Of the 20,022 interviewed persons with mortality follow-up, 6588 were ages 60 years and older and eligible to have cognitive function testing performed, 6339 of whom had valid cognitive function data. After excluding persons with missing data for any of the variables shown in Tables 1 to 3, 5903 persons aged 60 and older with complete data remained for mortality analyses. The length of follow-up of survivors ranged from 75 to 146 months (mean, 108 months; median, 107 months).

Physical Activity—Interview questions on LTPA were adapted from the 1985 National Health Interview Survey. Participants were asked, "In the past month did you...?" (Yes/No). If yes, "In the past month, how often did you...?" (Specify number of times), for the following: jogging or running, riding a bicycle or exercise bicycle, swimming, aerobic dancing, other dancing, calisthenics or floor exercises, gardening or yard work and weight

lifting (16). Open-ended questions assessed up to four other activities. Frequency of walking a mile or more also was asked. Persons responding "no times" to all of the aforementioned questions were classified "no LTPA." For LTPA rated at least moderate for age 60 or older, four groups of frequency of activity were formed (0, 1–4, 5–7, and 8+ times/week) to divide persons into similar-sized groups to facilitate analysis.

Cognitive Function—Questions assessing mental cognition were asked only of respondents aged 60 or older and not to proxy respondents. These questionnaires were designed for administration in a bilingual (English/Spanish) format so that respondents could be interviewed in their preferred language. The neuropsychological measures used in the NHANES III study were selected to assess cognitive functions typically affected in dementia. A short index cognitive function (SICF) was constructed for this analysis from these items administered both at home interview and again at a Mobile Examination Center to assess orientation, recall, and attention (17, 18). To minimize nonresponse in older persons, a home examination consisting of abbreviated set of measures similar to those performed was administered to 493 (8.3% of the sample for this analysis) participants who were unable or unwilling to come to a mobile examination center for a complete examination. Both examinations assessed memory function by use of the SICF. The SICF used consisted of six orientation, six recall, and five attention items. The six orientation items include general information such as the day of the week, the date, and participant's complete address including street, city/town, state and zip code (17). Each correct reply was scored one, with zero for an incorrect reply. Six recall items were tested in the home by naming three objects to the participant-"apple," "table," and "penny"-all of which were repeated immediately up to a maximum of six trials, and the number of trials required to learn the task were noted. Each correct response was scored as one with zero for an incorrect answer irrespective of the number of trials required to learn the objects. The subjects were asked to recall after 2 minutes of distracting tasks. Again, each object recalled correctly was scored one with zero for an incorrect answer.

Attention was evaluated in the home by asking the participant to recall up to five digits. The series of digits were selected from those used in the Weschler Adult Intelligence Scale (19). Each correct digit was scored as one for correct count or zero for wrong count. Thus, the overall scores on SICF calculated from these tests use the sum of orientation, recall, and attention and ranged from 0 to 17 with a median of 13, 25th percentile of 12, and 75th percentile of 16, i.e., skewed to the left. For analysis, four groups were formed by the use of these cut-points as shown in Table 1; quartiles with equal numbers of subjects could not be formed because of the skewed distribution and discrete nature of the variable.

Confounding Variables—During a home interview, an interviewer collected the demographic variables such as age, gender, and level of education used in this analysis. Health status was assessed as self-reported general health, the presence or absence of any history of major morbidity by physician diagnosis (heart attack, heart failure, stroke, medication for hypertension, diabetes, chronic bronchitis, emphysema, or nonskin cancer), and limitation of mobility (self-reported difficulty in climbing one flight of stairs or walking one-quarter mile with survey physician impression of mobility used to impute missing data). Potential confounding variables controlled for were age, sex, race/ethnicity (white, African American/black, Mexican American, other), education (<12 years, ≥ 12 years), Census region (South, other), urbanization (metropolitan area, other), health status (excellent/good, fair/poor), and chronic morbidity, alcohol use, and regular source of care at baseline. Additional potential confounders of LTPA were regular personal physician (yes/no), body mass index, systolic blood pressure, smoking, and log C-reactive protein. Measurement of blood pressure, height, weight, and serum analytes is described elsewhere (14).

Outcome Variables—National Center for Health Statistics conducted a mortality linkage of NHANES III participants with the National Death Index (20). The current linkage of the NHANES III includes deaths for adult participants occurring from the date of NHANES III interview through December 31, 2000. Information regarding the date of death and age of death was collected from matched death certificates. This process detected 2431 deaths in those in the present analysis. Efforts to link all NHANES III participants who died may have been unsuccessful in some cases. For details about NHANES III Linked Mortality Files, see http://www.cdc.gov/nchs/r&d/nchs_datalinkage/nhanes_data_linkage_activities.htm).

Statistical Analysis—Detailed descriptive statistics and measures of association were computed by use of the SUDAAN system (Version 9.0; Research Triangle Institute, Research Triangle Park, NC) to take into account the complex survey design in producing variance estimates with Taylor series linearization for variance estimation (21). Kaplan-Meier survival curves by LTPA and SICF category were computed with PROC KAPMEIER. Estimates of the risk of death derive from Cox proportional hazards regression models with time to event as the time scale computed with the SURVIVAL procedure in SUDAAN. Survivors were censored at the date of the end of mortality follow-up. An interaction term was initially included for LTPA frequency with SICF score. Two models were fit: Model I controlled for likely sociodemographic and health status confounders only and Model II for all confounders. Validity of the proportional hazards assumption was confirmed by inspection of un-weighted log negative log survival curves (22).

RESULTS

Among persons ages 60 and older in bivariate analyses, cognitive function was lower among the physically inactive: 31% (95% confidence interval [95% CI], 25–37) of those with no LTPA had SICF scores less than 12 compared with 16% (95% CI, 12–22) of those with 5 or more activities per week (p < .0001; Table 1). Mortality was also greatest among the inactive: 52% (95% CI, 48–57) compared with 26% (95% CI, 23–29) in the most active (p < .0001). Table 1 also shows age-adjusted prevalence of selected other characteristics by LTPA frequency. LTPA frequency was significantly associated with age, race/ethnicity, region, marital status, education, self-reported health status, mobility limitation, smoking, alcohol use, religious attendance, systolic blood pressure, and body mass index.

Kaplan Meier survival curves showed the poorest survival in those with LTPA 0 times/week and the best survival in those with LTPA > 0 times /week (Fig. 1; p < .01). Similarly, Kaplan-Meier survival curves for persons ages 60 and older at baseline showed the poorest survival in those in the lowest cognitive function category and the best survival in those in the highest category (not shown).

Next, proportional hazards regression models were fit to test for hypothesized interactions. No significant interaction was found for sex (p = .58), ethnicity (p = .57), or SICF score (p = .71) with LTPA frequency. However, a significant interaction with age (60–74 years vs. 75–90 years, p < .01) was noted. Therefore, further regression analysis of the association of LTPA frequency category with mortality during follow-up analysis was conducted separately for those ages 60 to 74 years and those 75 to 90.

Controlling for confounding by baseline demographic and socioeconomic variables and health status (Model 1), persons reporting activity more than eight times a week had only one half the risk of dying of those reporting no activity at ages 60 to 74 (Table 2) and less than two thirds the risk at 75 to 90 (Table 3). In this model, low cognitive function was also a significant predictor of mortality. Next, the effect of controlling for healthy behaviors and other risk factors was assessed. Tables 2 and 3 show that these variables explained none of

the effects of physical activity (Model II). At ages 60 to 74, there was a similarly reduced risk at any level of activity > 0 (even though test for trend p = .02), whereas a graded effect was suggested for ages 75 to 90 (test for trend p = .0005). However, low SICF score was no longer significantly related to mortality at ages 60–74 (test for trend 60–74, p = 0.57; 75 90, p = .03). Finally, we added the log concentration of HDL-cholesterol to Model II (not shown). This had essentially no effect on the hazard ratio for LTPA > 8 times per week at ages 60–74 (hazard ratio, 0.52, 95% CI, 0.35–0.78, p = .002) or 75–90 (HR, 0.65; 95% CI, 0.48–0.88, p = .006).

DISCUSSION

This analysis of data from the NHANES III linked-mortality file, a nationwide representative sample, is one of the first studies to provide population-based data on the association of cognitive function with LTPA and to test for interaction of cognitive function and LTPA as predictors of survival in older Americans. Both physical inactivity and poor cognitive function were found to independently predict poor survival chances during follow-up. However, no interaction of the two was detected. NHANES III data demonstrate that the risk of mortality was greater among persons with low compared with high cognitive function and low compared with greater LTPA even after controlling for confounding by baseline health status and mobility and health behaviors, supporting the hypothesis of an independent association. The association of LTPA with mortality did not differ by sex or race/ethnicity but varied by age, the effect being greater at 60 to 74 than 75 years or greater. The greater effect of SICF score at 75 years or greater than 60 to 74 years should be explored in future studies with the use of more nuanced measures for cognitive function that can exclude possible ceiling effects and insensitivity to gradations of performance in non-demented persons.

Mechanisms by which low cognitive function or dementia adversely affect mortality remain obscure; in most studies, the effect cannot be fully explained by adjusting for comorbidity, functional status, or sociodemographic variables (4 7, 23, 24). It has been hypothesized that a high level of LTPA may slow cognitive decline through its actions to raise high-density lipoprotein cholesterol, lower systolic blood pressure, and generally improve the cardiovascular risk profile. The present study indicates that although LTPA is inversely associated with SICF scores, excess mortality associated with lack of LTPA is not explained by cognitive dysfunction nor was there an interaction of the two variables. However, the effect persisted even after controlling for multiple cardiovascular risk factors. We were not able to find support for LTPA protecting against adverse effects of low SICF on mortality.

The NHANES III linked-mortality file provides population-based data on the association of LTPA, cognitive function, and survival in a nationwide representative sample of Americans. Oversampling of persons aged 60 and older permitted reliable estimates for this group. Over-sampling of Mexican Americans permitted estimates for this group, which comprised only about 2% of the population older than 60 at the time of the survey (Table 1). However, several unavoidable limitations of the present study include possible bias arising from survey nonresponse and missing values for some variables and from possible changes in LTPA and cognitive function and/or other variables during the follow-up period. Several special studies of NHANES III data have indicated little bias caused by nonresponse (25). Comparison of vital status and demographics of the analysis sample and those excluded for missing data but eligible for follow-up revealed those excluded were more likely to be female, Mexican American, in poor health, and to die during the follow-up. Thus, selection bias cannot be excluded. Duration of LTPA was not recorded, so caloric expenditure per week could not be computed. Occupational physical activity was not measured, but most persons older than 60 years of age were retired, especially in the 75 years or older group.

SICF is an indicator of memory and orientation. Different results may have been obtained had other dimensions of cognitive function been studied. Temporal sequence cannot be ascertained for the association of LTPA and SICF. The representativeness of the sample and the use of sample weights provide generalizability of the results to the United States noninstitutionalized population of the same ages. Data from longitudinal studies with measures of multiple dimensions of physical activity and cognition would be helpful in delineating mechanisms involved.

CONCLUSION

In a nationwide cohort of Americans, analyses demonstrated a greater risk of death independent of confounders among those with low LTPA or low cognitive function compared to others. No interaction of the two was found.

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Selected Abbreviations and Acronyms

LTPA	leisure-time physical activity
NHANES III	Third National Health and Nutritional Examination Survey
SICF	short index cognitive function
95% CI	95% confidence interval

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Kaplan-Meier survival curves for persons aged 60 years and older by leisure-time physical activity level at baseline.

TABLE 1

Age-adjusted prevalence (%) of selected characteristics by activity level in persons aged 60 years and older

	Leisu	ire-time	physica	l activit	y (times	/week)
	Total	0	1-4	5-8	8 <	<i>p</i> value
u	5903	1812	1861	1068	1162	
Dead	2429	52	29	28	26	< .000
Cognitive function index						
<12	1809	31	19	16	16	< .000
12–13	1946	33	39	32	38	
14–16	1168	19	18	24	22	
17	980	17	24	28	23	
Female	3119	71	55	53	50	< .000
Age 80+ years	1512	24	10	13	6	< .000
Mexican American	1017	ю	7	7	-	< .000
African American	1122	13	×	9	5	< .000
South region	2465	38	35	23	23	< .000
Metropolitan residence	2487	43	39	49	51	< .000
Unmarried	2693	56	38	36	35	< .000
Education < 12 years	3358	56	45	36	30	< .000
Fair-poor health	2139	57	28	22	16	< .000
≥1 chronic illness	3515	67	59	50	51	< .000
Mobility limitation	2081	45	27	26	19	< .000
Current smoking	912	19	17	14	13	< .000
Alcohol in past month	1425	16	30	35	37	< .000
No regular physician	686	15	15	16	15	< .906
No religious attendance	1896	45	34	33	29	< .000
Systolic BP $\ge 140 \text{ mm Hg}$	2699	44	49	53	49	.001
BMI $\ge 25 \text{ kg/m}^2$	3076	46	53	48	45	.017
BMI = body mass index.						
p values from weighted Chi-so	quare test	s.				

TABLE 2

Adjusted hazards ratios (95% CIs) of SICF score and LTPA frequency for mortality from all causes among persons ages 60 to 74 years in NHANES III

	Model 1		Model 2	
Variable	Hazard ratio	95% CI	Hazard ratio	95% CI
LTPA (times/wk)				
0	1.00		1.00	
1-4	0.51 ^a	0.41-0.64	0.47 ^a	0.37-0.60
5–8	0.54 ^{<i>a</i>}	0.38-0.76	0.48 ^{<i>a</i>}	0.33-0.68
> 8	0.51 ^a	0.38-0.76	0.5 ^{<i>a</i>}	0.35-0.78
SICF score				
17	1.00		1.00	
14–16	0.95	0.61-1.48	0.9	0.59–1.4
12–13	0.93	0.70–1.3	0.85	0.60-1.20
0–11	1.36 ^b	1.00-1.84	1.19	0.83-1.71
Age, years	1.07 ^a	1.05-1.10	1.07 ^a	1.05-1.10
Sex, male	1.70 ^{<i>a</i>}	1.45-2.00	1.82 ^{<i>a</i>}	1.492.22
Race/ethnicity				
AA	0.98	0.80-1.20	1.04	0.81-1.33
MA	0.76 ^b	0.57-1.00	1.01	0.72-1.43
Education, less than high school	0.90	0.69–1.17	0.85	0.61-1.19
South region	0.90	0.70-1.16	0.88	0.66–1.17
Urbanized	1.07	0.84-1.36	1.00	0.77-1.28
Self-reported health F/P	1.85 ^{<i>a</i>}	1.47-2.33	1.63 ^{<i>a</i>}	1.26-2.11
Morbidity	1.73 ^{<i>a</i>}	1.39–2.15	1.57 ^a	1.23-2.00
Limited mobility	1.20	0.99–1.46	1.48 ^{<i>a</i>}	1.20-1.83
Systolic blood pressure, mm Hg			1.00	1.00-1.00
Body mass index, kg/m ²			0.95 ^a	0.92-0.98
Smoking				
Current			2.14 ^a	1.58-2.90
Former			1.55 ^a	1.18-2.06
Alcohol use, yes			0.84	0.62-1.14
Reg. physician, yes			1.03	0.78-1.36
Ln CRP			1.29 ^a	1.14-1.46

AA = African American; P5% CI = confidence interval; CRP = C-reactive protein; MA = Mexican American; F/P = fair-poor; Reg. = regular care by personal physician; SICF = short index of cognitive function.

 $a p \le .01.$

 $^{b}p < .05.$

TABLE 3

Adjusted hazards ratios (95% CIs) of SICF and LTPA frequency for mortality from all causes among persons aged 75+ years in NHANES III

	M	lodel 1	M	lodel 2
Variable	HR	95% CI	HR	95% CI
LTPA (times/wk)				
0	1.00		1.00	
1–4	0.83 ^b	0.69–1.00	0.88	0.73-1.07
5–8	0.69 ^a	0.56-0.85	0.66 ^a	0.49–0.87
> 8	0.63 ^a	0.48-0.83	0.66 ^a	0.49–0.89
SICF score				
17	1.00		1.00	
14–16	1.36	0.98-1.88	1.37	0.94-2.01
12–13	1.27	0.92 - 1.74	1.33	0.90-1.97
0-11	1.51 ^a	1.15-1.98	1.53 ^b	1.11-2.09
Age, years	1.08 ^a	1.06-1.11	1.08 ^a	1.05-1.11
Sex, male	1.74 ^a	1.49-2.03	1.85 ^a	1.55-2.21
Race/ethnicity				
AA	0.91	0.76-1.09	0.81	0.62-1.07
MA	0.58 ^a	0.43-0.79	0.53 ^a	0.35-0.80
Education, less than high school	1.08	0.97-1.20	1.06	0.92-1.21
South region	0.92	0.72-1.18	0.89	0.67-1.19
Urbanized	1.02	0.84-1.24	1.08	0.85-1.36
Self-reported health F/P	1.31 ^a	1.16–1.49	1.27 ^a	1.09–1.48
Morbidity	1.34 ^a	1.17-1.55	1.29 ^a	1.07-1.56
Limited mobility	1.16	0.97–1.39	1.21 ^b	1.00-1.45
Systolic blood pressure, mm Hg			1.00	1.00-1.00
Body mass index, kg/m ²			0.96 ^a	0.94-0.98
Smoking				
Current			1.29	0.99–1.69
Former			1.16	0.98-1.38
Alcohol use, yes			1.00	
Reg. physician, yes			1.05	0.82-1.35
Ln CRP			1.21 ^{<i>a</i>}	1.07-1.36

AA = African American; P5% CI = confidence interval; CRP = C-reactive protein; MA = Mexican American; F/P = fair-poor; Reg. = regular care by personal physician; SICF = short index of cognitive function.

 $a p \leq .01.$

^b_{p < .05.}