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Original article

Leisure-time physical activity and mortality in a multiethnic prospective cohort study: the Northern Manhattan Study

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ABSTRACT

Purpose: To examine whether the survival benefit of exercise is modified by obesity.
Methods: In the Northern Manhattan Study, we collected baseline sociodemographics and cardiovascular disease risk factors. The primary exposure was leisure-time physical activity (LTPA) and the outcomes were total, vascular, and nonvascular deaths (non-VaD). LTPA was defined as any versus none and metabolic equivalent score category (total activity weighted by intensity). We used Cox models to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs).
Results: A total of 3298 participants (mean age 69 years, 52% Hispanic, 63% women) were followed over a mean of 11.8 years with 1589 total deaths (641 vascular, 819 nonvascular). Any activity (adjusted HR: 0.84, 95% CI: 0.75–0.94) was associated with reduced risk of all-cause mortality and non-VaD, but not VaD. We found an interaction ($P < .05$) of LTPA with body mass index (BMI) less than 30 for all-cause and vascular mortality. Any LTPA was associated with reduced all-cause mortality (adjusted HR: 0.77, 95% CI: 0.68–0.87) and VaD (adjusted HR: 0.79, 95% CI: 0.65–0.97) only among those with BMI less than 30.
Conclusions: We found no evidence of an independent survival benefit of LTPA among those with BMI more than 30. The health benefits of exercise should be considered in the context of obesity.

Introduction

The adoption of a healthy lifestyle is associated with multiple benefits, notably a reduction in incident coronary heart disease and stroke [1,2]. These benefits extend to cardiovascular disease mortality [3], all-cause mortality [4], and cognitive function [5,6], and the effect extends throughout the life span indicating that "it is never too late to start" [7]. The effects on nonvascular mortality, such as cancer, however have not been as well established. The components of a healthy life have been variably delineated by different organizations and epidemiologic studies, although common to most recommendations is a program of regular leisure-time physical activity (LTPA). The benefits of a regular physical activity program influence multiple biological and emotional pathways that ultimately translate to health benefits across multiple diseases. Physical activity is also an integral component in the lifestyle modifications recommended for the control of cardiovascular disease risk factors [8–10] and prevention of other chronic health conditions [11]. Physical activity also independently influences multiple biological processes, leading to a more beneficial profile in inflammatory and coagulation cascades, as well as improved endothelial cell function [12].

Although the benefits of physical activity have been well established, there are less data on whether the effects could be modified by other known risk factors. In one study, for example, active smokers did not have a protective effect on coronary heart disease from LTPA [13]. In another study, the effect of physical activity on cardiovascular disease was present among individuals with recommended, as well as elevated, body mass indices (BMIs), leading to the concept of the "healthy obese" [14]. This construct, however, has been called into question [15]. These prior studies have rarely included urban dwelling-elderly and Hispanic populations, two segments of the population in whom the obesity epidemic has not abated and physical inactivity is common [16,17].

No potential conflicts of interest relevant to this article were reported.

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In our study, we explored the association of physical activity with vascular and nonvascular mortality in an urban dwelling triethnic population. We hypothesized that those who were obese would have a lesser protective effect from physical activity on risk of mortality compared with the nonobese.

Methods

Recruitment of the cohort

The Northern Manhattan Study (NOMAS) is a population-based study designed to evaluate the impact of medical, socioeconomic, and other risk factors on the incidence of vascular disease in a stroke-free cohort. Participants were identified by dual-frame random digit dialing in Northern Manhattan as previously described [18] and were eligible if they met the following criteria: (1) had never been diagnosed with a stroke; (2) were more than the age of 39 years; and (3) resided in Northern Manhattan for 3 months or more in a household with a telephone. The study was approved by the Institutional Review Boards at Columbia University Medical Center and the University of Miami. All participants gave informed consent to participate in the study.

Assessments at enrollment of the cohort

Baseline status and risk factors were collected through interviews of participants by trained bilingual research assistants. Physical examinations and in-person measurements were carried out by study physicians; fasting blood specimen phlebotomy was performed by study nurses. Race-ethnicity was determined by self-identification in response to a questionnaire modeled after the 2000 U.S. Census. Education was classified as completing high school versus not. Standardized questions were adapted from the Behavioral Risk Factor Surveillance System regarding the following conditions: hypertension, diabetes, and cigarette smoking. Standard techniques were used to measure blood pressure, height, weight, and fasting glucose and lipid panels as previously described [19]. Obesity was defined as a BMI more than 30. Hypertension was defined as blood pressure 140 mm Hg/90 mm Hg or more, a physician diagnosis of hypertension or a patient's self-report. Diabetes mellitus was defined as fasting blood glucose 126 mg/dL or more or the patient's self-report. Fasting blood samples were obtained and lipid profile was measured as previously described. Alcohol intake was ascertained with the use of previously validated questionnaires.

LTPA was measured using an in-person questionnaire adapted from the National Health Interview Survey of the National Center for Health Statistics [20]; it records the duration and frequency of various leisure-time activities for the 2 weeks before the interview. Participants who reported no physical activity were coded as inactive. For each activity, we obtained duration and frequency and if duration of activity was less than 10 minutes, it was coded as "no activity". This questionnaire has been previously reported as reliable and valid in this population [18]. This same measure also correlated with BMI, activities of daily living scores, and activity scores on a quality of well-being scale. Objective measures of physical fitness, moreover, as measured by exercise and treadmill testing or maximum oxygen uptake correlate well with physical activity questionnaires [21]. The participants' responses were correlated with compendia of physical activity to categorize the intensity of each activity in metabolic equivalents (MET) [22]. Total activity was summarized via the MET-score, whereby the MET for each individual activity is multiplied by the frequency per week and duration [23].

Follow-up and outcome measures

Participants are followed annually via phone screening to detect any new cardiac or neurologic symptoms, interval hospitalizations, medical conditions, or death. Complete loss to follow-up is present in less than 1% and is not associated with race-ethnicity [24]. Cause of death was ascertained through information gathered from the participant's family, review of medical records, and a copy of the death certificate if available. All-cause mortality was further divided into VaD and non-VaD. VaD included underlying heart disease (myocardial infarction, sudden cardiac death, congestive heart failure, and other cardiac arrhythmias), stroke, and pulmonary emboli.

Statistical analysis

Baseline characteristics were calculated as means for continuous variables and proportions for categorical variables. The 10-year cumulative risks of death were calculated using Kaplan-Meier method. The primary outcome was all-cause mortality, and the secondary outcomes were VaD and non-VaD; if cause of death could not be defined as VaD or non-vaD, participants were excluded from the secondary analyses. The primary exposure of interest was LTPA categorized as (1) any physical inactivity versus none and (2) quartiles of the MET-score weighted by total activity intensity. Because 40.8% of our cohort participants were physically inactive, we categorized the MET-score into three groups: the physically inactive as a reference (40.8%), intermediate level of MET-score (35.8%), and the highest level of MET-score (23.8%). Cox proportional hazard models were fitted to calculate hazard ratios (HRs) and 95% confidence interval (CI) for the association of LTPA with the risk of total mortality, non-VaD, and VaD. The models were unadjusted and fully adjusted for confounders including demographics (age, sex, and education) and cardiovascular disease risk factors (BMI, tobacco use, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, moderate alcohol consumption, hypertension, diabetes, and prior heart disease). We tested for interactions between physical activity with baseline sociodemographic and cardiovascular disease risk factors ran stratified models when the *P* for interaction was less than .05. Improvement of model fit including the interactions with the three categories of MET-score was tested using a χ^2 test with 2 degrees of freedom. The proportionality assumption was examined in all models. All statistical analyses were performed with SAS, version 9.3 (SAS Institute Inc., Cary, NC).

Results

Baseline demographics of our cohort are outlined in Table 1. Briefly, 40.8% of our sample was physically inactive and 52.4% were Hispanics, 62.8% women, and 72.5% had BMI less than 30. Over a mean 11.8 years of follow-up (minimum <1 year, maximum 20.5 years, interquartile range 8.4–15.1 years), there were 1589 deaths of which 641 were VaD, 819 were non-VaD, and 129 with insufficient data to classify. The 10-year cumulative risk probabilities of death were .30 (95% CI: 0.28–0.32) overall, .28 (95% CI: 0.26–0.30) for any LTPA group, and .32 (95% CI: 0.30–0.35) for no LTPA group (*P* for the difference between any LTPA vs. none = .013).

Physical activity and risk of all-cause mortality, non-VaD, and VaD

Table 2 provides unadjusted and fully adjusted associations of physical activity with mortality. In unadjusted analyses, any

Table 1
Baseline demographics of the NOMAS

Variable	Entire cohort ($n = 3298$)	No LTPA ($n = 1345$)	Any LTPA ($n = 1953$)	*P*-value difference
	Mean (SD) or *n* (%)			
Sociodemographic characteristics				
Age (y)	69.2 (10.3)	69.3 (10.3)	69.3 (10.3)	.2
Women	2071 (62.8%)	897 (66.7%)	1174 (60.1%)	.001
Men	1227 (37.2%)	448 (33.3%)	779 (39.9%)	reference
Race-ethnicity				
Hispanic	1728 (52.4%)	835 (62.1%)	893 (45.7%)	<.0001
Non-Hispanic black	803 (24.3%)	269 (20%)	534 (27.3%)	.3
Non-Hispanic white	690 (20.9%)	213 (15.8%)	477 (24.4%)	reference
Less than high school education	1786 (54.2%)	840 (62.5%)	1007 (51.6%)	<.0001
Medicaid or no insurance	1435 (43.8%)	687 (51.3%)	748 (38.6%)	<.0001
Medical comorbidities				
Tobacco use				
Never used	1545 (46.8%)	624 (46.4%)	921 (47.2%)	reference
Former smoker	1191 (36.1%)	478 (35.6%)	713 (36.5%)	.9
Current user	560 (17.0%)	242 (18.0%)	318 (16.3%)	.2
Alcohol use				
Never or heavy	2212 (67.1%)	976 (72.6%)	1236 (63.3%)	<.001
Mild-moderate*	1086 (32.7%)	369 (27.4%)	717 (36.7%)	reference
Hypertension	2429 (73.7%)	1017 (75.6%)	1412 (72.3%)	.03
Diabetes mellitus	716 (21.7%)	324 (24.2%)	392 (20.1%)	.005
Low-density lipoprotein cholesterol (mg/dL)	129 (36)	129 (36)	129 (36)	.4
High-density lipoprotein cholesterol (mg/dL)	46 (15)	46 (14)	48 (15)	.0002
BMI $\geq$ 30	901 (27.5%)	404 (30.3%)	497 (25.5%)	.003
BMI < 30	2379 (72.5%)	929 (69.7%)	1450 (74.5%)	reference

* Less than 2 servings of alcoholic beverages per day.

physical activity versus none was associated with a lower risk of all-cause, as well as non-VaD, mortality. The associations remained significant after adjusting for baseline demographics and other cardiovascular disease risk factors. We found similar results when LTPA was analyzed as categories of MET-score for all of our outcomes (Table 3).

Effect modification of increased BMI on the association of physical activity with the risk of non-VaD and VaD

We tested for interactions between LTPA and baseline cardiovascular disease risk factors to further investigate for effect modification. There was evidence of an interaction between performing any activity and BMI less than 30 versus 30 or more with all-cause mortality (*P* for interaction = .01) and VaD (*P* for interaction = .02), but not for non-VaD. We found a similar statistical interaction for the categories of the MET-score with BMI less than 30 versus 30 or more (χ^2 test with 2 degrees of freedom, *P* for interaction = .04). In summary, compared with none, performing any LTPA was associated with lower risk of all-cause mortality and being in the highest category of the MET-score was associated with lower risk of VaD. These findings, however, were only seen, among those with a BMI less than 30 and not in those with a BMI 30 or more (Table 4). We did not find evidence of an interaction between baseline sociodemographics and cardiovascular disease risk factors with LTPA on mortality risk. We carried out further analyses excluding participants with malignancy (excluding skin cancers, $n = 349$) and any heart disease ($n = 431$), and the magnitude of associations in all analyses were unchanged (Supplemental Tables 1–3).

Discussion

In our prospective cohort of elderly, multiethnic, urban-dwelling individuals, we found that LTPA was associated with a lower risk of all-cause mortality and non-VaD, but not with a lower risk of VaD. Our study further tested the concept of the "metabolically healthy obese" or "fit but fat" [25,26]. The protective effect of LTPA on all-cause mortality has been well characterized in multiple prospective cohort studies [27], as has the effect on VaD [28]. We, however, found lack of association between LTPA and VaD, and, moreover, effect modification by obesity, such that protective effect of LPTA on VaD risk was mitigated in the presence of an elevated BMI. Our results call into question the commonly held perception of "fit but fat," and argue that this group in the population also has a high risk of mortality. Our results should be interpreted with caution although, as they are intended to indicate that those with an elevated BMI should still continue to perform LTPA, as they gain an advantage in all-cause mortality. In a related manner, LTPA is insufficient at protecting against VaD alone, and high risk individuals should have a multifaceted treatment approach targeted at "life's simple 7's" including consideration of weight, diet, and modification of cardiovascular disease risk factors as a whole [29].

The protective effect of LTPA on VaD among those with lower BMI is likely to be related to two different physiological processes (independent or through other risk factors) leading to a reduction of myocardial infarction, stroke, and sudden cardiac death. A common finding is that LTPA improves the control of several

Table 2
Association of LTPA (any activity vs. none) with all-cause mortality ($n = 1589$), non-VaD ($n = 819$), and VaD ($n = 641$) in the NOMAS*

Physical activity classification	All-cause mortality, HR (95% CI)	Non-VaD, HR (95% CI)	VaD, HR (95% CI)
Any LTPA versus none (univariate)	0.87 (0.79–0.96)	0.87 (0.79–0.96)	0.89 (0.77–1.05)
Any LTPA versus none (multivariable)†	0.84 (0.75–0.94)	0.84 (0.75–0.94)	0.90 (0.76–1.08)

* One hundred twenty-nine deaths with insufficient documentation to classify the cause of death

† Adjusted for age, race-ethnicity, high school education, health insurance, moderate alcohol use, tobacco use, hypertension, diabetes, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, BMI, and any heart disease.

Table 3
Association of LTPA (MET-score) with all-cause mortality, non-VaD, and VaD in the NOMAS

Physical activity classification	All-cause mortality, HR (95% CI)	Non-VaD, HR (95% CI)	VaD, HR (95% CI)
Third quartile of MET-score versus no activity (univariate)	0.87 (0.78–0.97)	0.84 (0.71–0.98)	0.89 (0.75–1.07)
Fourth quartile of MET-score versus no activity (univariate)	0.87 (0.77–0.99)	0.86 (0.73–1.03)	0.91 (0.74–1.11)
Third quartile of MET-score (range) versus no activity[*,†]	0.87 (0.77–0.98)	0.83 (0.70–0.98)	0.92 (0.75–1.11)
Fourth quartile of MET-score (range) versus no activity[*,†]	0.79 (0.69–0.91)	0.75 (0.62–0.91)	0.89 (0.71–1.10)

[*] Adjusted for age, race-ethnicity, high school education, health insurance, moderate alcohol use, tobacco use, hypertension, diabetes, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, BMI, and any heart disease.
[†] *P*-value for the improvement of fit with χ^2 test with 2 degrees of freedom is .003 for all-cause mortality, .01 for non-VaD, and .51 for VaD.

other modifiable risk factors, such as hypertension [30] and diabetes [31], thereby reducing vascular mortality. This is likely to be an important component of the effect of LTPA, and in recently completed analyses, LTPA had a similar protective effect to taking medications for chronic cardiovascular disease risk factors [32]. In our study, however, the protective effect of LTPA on VaD among those with a low BMI remained after adjusting for other cardiovascular disease risk factors. LTPA also has independent effects from modulation of traditional risk factors, notably by improving inflammatory biomarker profiles and improvement in endothelial function and vascular reactivity [33,34]. These latter processes may explain, in part, the protective effect of LTPA on non-VaD and all-cause mortality regardless of BMI. In a recent meta-analysis, LTPA was found to have a potential protective effect on breast and colon cancer, with the effect in part explained by changes in inflammatory and glucose homeostasis pathways [35]. It is unclear, however, to what degree modulating these pathways with LTPA alters the natural history of malignant cells and the associated immune response, as opposed to protecting against incident cardiovascular disease events in patients with cancer. These mechanistic pathways should be explored in further detail in future studies.

In our study, we also found that the survival benefit from LTPA did not extend to those with an elevated BMI. The reasons for this observation may be related to several unique aspects of our study. In the NOMAS, we have a high proportion of participants who have not completed high school and are underinsured (Medicaid or no insurance). Both factors were associated with higher vascular disease mortality risk due to psychosocial stressors or impact of vascular disease risk factors, and these may not be easily overcome by heathy lifestyle such as LTPA [36]. In a prior analysis, we showed that LTPA was protective against markers of subclinical cerebrovascular disease only among those patients who had health insurance which is a proxy for access to care or socioeconomic status in our cohort [37]. Our prospective cohort study also has a high proportion of elderly participants, including close to a quarter being more than the age of 75 years (data not shown), and traditional cardiovascular disease risk factors may not be as strongly associated with outcomes in the geriatric population [38]. Finally, in the elderly misclassification in the cause of death may occur, which in our study would influence the protective effect on VaD versus non-VaD, but not mortality overall.

Our study has several limitations. As with any study using self-reported data, the possibility of over-reporting LTPA may lead to misclassification bias. Study participants are likely to over-report, and not under-report, the amount and intensity of activity performed, which would likely lead to an underestimate of the protective effect of LTPA. We examined one measure of physical activity and BMI at enrollment, rather than longitudinal activity and changes, which may not allow us to capture declines in physical activity associated with frailty and subsequent mortality [39]. The NOMAS did not systematically capture non-LTPA, such as activity with work or commuting, although there is an independent effect of activity performed to improve fitness and health rather than for employment [40]. We also did not capture objective measures of fitness or sedentary behavior using accelerometers or cardiopulmonary exercise testing, which may limit our ability to fully capture the extent of physical activity or the independent effect of total sedentary time. Nonetheless, using a simple self-report questionnaire that mimics questions performed in routine clinical use, we have been able to demonstrate a survival benefit in a sample of older adults. Our study also did not collect important information on other confounders in the association between LTPA and mortality, notably socioeconomic status, household income, type of employment, self-classification of race within Hispanics, and insulin resistance among others. In NOMAS, the sample size may be insufficient to detect more subtle protective effects from LTPA against VaD and in other analyses including by race-ethnicity or other baseline demographics. Finally, the results of our study may not be generalizable to other populations.

Our study has important strengths, including a sample of older, predominantly Hispanic participants for whom less is known regarding risk of mortality, low loss to follow-up, and comprehensive assessment of causes of death.

In conclusion, we found that LTPA was protective against all-cause mortality, whereas for VaD the protective effect was present only among those who are not obese. Overall however, the protective effects across multiple health domains from LTPA are clear, and all individuals should be encouraged to maintain a lifetime of physical activity across the age spectrum.

Table 4
Association of LTPA (any vs. none) with all-cause mortality, non-VaD, and VaD in the NOMAS based on BMI

Physical activity classification		All-cause mortality[*], adjusted HR (95% CI)	Non-VaD, adjusted HR (95% CI)	VaD[*], adjusted HR (95% CI)
BMI $<$ 30	Any LTPA versus none[†]	0.77 (0.68–0.88)	0.76 (0.64–0.91)	0.80 (0.65–0.97)
	Third quartile of MET-score versus no activity[†]	0.81 (0.71–0.93)	0.79 (0.65–0.96)	0.82 (0.66–1.04)
	Fourth quartile of MET-score versus no activity[†]	0.70 (0.59–0.83)	0.73 (0.59–0.90)	0.75 (0.59–0.97)
BMI $\geq$ 30	Any LTPA versus none[†]	1.07 (0.86–1.34)	0.93 (0.68–1.28)	1.27 (0.91–1.79)
	Third quartile of MET-score versus no activity[†]	1.08 (0.84–1.38)	0.98 (0.69–1.39)	1.19 (0.81–1.74)
	Fourth quartile of MET-score versus no activity[†]	1.06 (0.79–1.43)	0.84 (0.54–1.31)	1.43 (0.93–2.20)

[*] *P* for interactions between LPTA and BMI less than 30 versus 30 or more were less than .05.
[†] Adjusted for age, race-ethnicity, high school education, health insurance, moderate alcohol use, tobacco use, hypertension, diabetes, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and any heart disease.

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Appendix

Supplemental Table 1
Association of LTPA (any activity vs. none) with all-cause mortality, non-VaD, and VaD in the NOMAS excluding those with baseline history of malignancy and any heart disease ($n = 780$)

Physical activity classification	All-cause mortality, HR (95% CI)	Non-VaD, HR (95% CI)	VaD, HR (95% CI)
Any LTPA versus none (univariate)	0.91 (0.80–1.02)	0.86 (0.73–1.02)	0.99 (0.82–1.21)
Any LTPA versus none (multivariable)*	0.84 (0.74–0.96)	0.82 (0.68–0.99)	0.93 (0.75–1.15)

* Adjusted for age, race-ethnicity, high school education, health insurance, moderate alcohol use, tobacco use, hypertension, diabetes, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, body mass index any heart disease.

Supplemental Table 2
Association of LTPA (MET-score) with all-cause mortality, non-VaD, and VaD in the NOMAS excluding baseline malignancy and any heart disease ($n = 780$).

Physical activity classification	All-cause mortality, HR (95% CI)	Non-VaD, HR (95% CI)	VaD, HR (95% CI)
Third quartile of MET-score versus no activity (univariate)	0.90 (0.79–1.03)	0.82 (0.68–0.99)	1.03 (0.83–1.27)
Fourth quartile of MET-score versus no activity (univariate)	0.92 (0.79–1.07)	0.94 (0.76–1.16)	0.95 (0.74–1.22)
Third quartile of MET-score (range) versus no activity*	0.86 (0.75–1.00)	0.82 (0.67–1.01)	0.97 (0.76–1.22)
Fourth quartile of MET-score (range) versus no activity*	0.81 (0.69–0.96)	0.83 (0.66–1.04)	0.88 (0.68–1.16)

* Adjusted for age, race-ethnicity, high school education, health insurance, moderate alcohol use, tobacco use, hypertension, diabetes, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

Supplemental Table 3
Association of LTPA stratified by BMI with all-cause mortality, non-VaD, and VaD in the NOMAS excluding baseline malignancy and any heart disease ($n = 780$).

Physical activity classification	All-cause mortality, adjusted HR (95% CI)	Non-VaD, adjusted HR (95% CI)	VaD, adjusted HR (95% CI)
BMI < 30			
Any LTPA versus none*	0.77 (0.66–0.89)	0.77 (0.63–0.94)	0.80 (0.65–0.97)
Third quartile of MET-score versus no activity*	0.79 (0.67–0.94)	0.75 (0.59–0.96)	0.89 (0.68–1.17)
Fourth quartile of MET-score versus no activity*	0.74 (0.61–0.89)	0.79 (0.61–1.02)	0.74 (0.54–1.02)
BMI ≥ 30			
Any LTPA versus none *	1.11 (0.85–1.46)	1.02 (0.70–1.48)	1.29 (0.85–1.95)
Third quartile of MET-score versus no activity*	1.11 (0.83–1.50)	1.05 (0.70–1.59)	1.19 (0.75–1.90)
Fourth quartile of MET-score versus no activity*	1.09 (0.77–1.55)	0.96 (0.58–1.59)	1.46 (0.88–2.45)

P for interactions between LPTA and BMI less than 30 versus 30 or more were less than .05 only for all-cause mortality and vascular mortality with the MET-score.

* Adjusted for age, race-ethnicity, high school education, health insurance, moderate alcohol use, tobacco use, hypertension, diabetes, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.