Incident Diabetes Mellitus, Hypertension, and Cardiovascular Disease Risk in Exercising Hypercholesterolemic Patients

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Exercise may be an important treatment for hypercholesterolemic patients, particularly in statin users who are at increased diabetes risk. We therefore used Cox proportional hazard analyses to compare running and walking dose (metabolic equivalent hours/day [MET-h/d]) to diabetes, hypertension, and cardiovascular disease (CVD) risk in hypercholesterolemic patients. There were 60 diabetic- and 373 CVD-related deaths during a 10.1-year mortality surveillance of 6,688 hypercholesterolemic patients. In addition, there were 177 incident nonfatal diabetes, 815 incident nonfatal hypertensions, and 323 incident nonfatal CVD events during a 6.4-year follow-up of 6,971 hypercholesterolemic patients who supplied follow-up questionnaires. Fatal and nonfatal diabetes risk decreased 26% ($p = 0.002$) and 19% ($p \leq 0.0001$) per MET-h/d, respectively, and relative to <1.07 MET-h/d decreased 35% ($p = 0.19$) and 55% ($p \leq 0.0001$), respectively, for 1.8 to 3.6 MET-h/d and 73% ($p = 0.02$) and 71% ($p \leq 0.0001$), respectively, for ≥3.6 MET-h/d. Fatal and nonfatal CVD risk decreased 8% ($p = 0.008$) and 3% ($p = 0.22$) per MET-h/d, respectively, and relative to <1.07 MET-h/d decreased 10% ($p = 0.45$) and 36% ($p = 0.008$) for 1.8 to 3.6 MET-h/d, respectively, and 37% ($p = 0.009$) and 26% ($p = 0.10$), respectively, for ≥3.6 MET-h/d. Incident hypertension risk decreased 4% ($p = 0.01$) per MET-h/d, and relative to <1.07 MET-h/d decreased 29% ($p = 0.002$) for 1.8 to 3.6 MET-h/d and 31% ($p = 0.001$) for ≥3.6 MET-h/d. In conclusion, running and walking for exercise lowers diabetes, hypertension, and CVD risk in hypercholesterolemic patients and should more than compensate for the purported 9% increase in diabetes risk from statin use. By preventing morbidity and mortality for a specific existing medical condition, some exercise expenses may qualify for flexible spending account expenditures in hypercholesterolemic patients when prescribed by a physician. Published by Elsevier Inc. (Am J Cardiol 2015;116:1516−1520)

Hypercholesterolemic patients are at high risk for both cardiovascular disease (CVD) and hypertension.[1] High cholesterol per se may increase the risk of hypertension by limiting the bioavailability of nitric acid, causing endothelial dysfunction, and enhancing the activity of the angiotensin-aldosterone system.[2] Randomized controlled trials report that statins reduce the risks for cardiac events by 20% to 44%,[3−5] however, statins also increase diabetes risk by about 9%.[6] Running and walking are associated with reduced risk for hypertension, hypercholesterolemia, diabetes, and CVD.[7−11] Mitigating hypertension, diabetes, and other risk factors in hypercholesterolemic patients is important because the contribution of individual risk factors to CVD risk appears to be multiplicative rather than additive.[12] Although antidiabetic and antihypertensive drugs are usually covered by insurance, flexible spending accounts (FSA), and medical saving accounts (MSA), their prevention by exercise is not. However, some exercise costs may qualify for FSA and MSA reimbursement if prescribed by a physician for the treatment of a specific disease or medical condition.[13,14] We therefore examined the relation of running and walking to disease risk in hypercholesterolemic patients to characterize the dose−response relationships and clarify the exercise dosage needed to compensate for statin-induced diabetes risk. The results are germane to the 30 million adults in the United States who run ≥50 times per year[15] and the 54 million who reported running at least once in 2013.[15]

Methods

The National Death Index[16] was used to perform mortality surveillance of the National Runners' Health Study I (54,956 runners recruited from 1991 to 1994), the National Runners' Health Study II (63,308 runners recruited from 1998 to 2001), and the National Walkers' Health Study (42,140 walkers recruited from 1998 to 2001).[8−11] In addition, 80% of the surviving National Runners' Health Study I participants provided follow-up surveys. The 63,308 runners of the National Runners' Health Study II and the 42,140 walkers of the National Walkers' Health Study partially were resurveyed in 2006 to establish a population of approximately 50,000 runners and walkers for a proposed

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Table 1
Baseline characteristics of hypercholesterolemic patients and non-hypercholesterolemic controls (Percent or mean±SD)

Analyses:	Nonfatal events (Follow-up survey)			Fatal events (mortality surveillance)		
Group:	Hypercholesterolemic patients		Controls	Hypercholesterolemic patients		Controls
	All	Statin users	All	All	Statin users	All
Sample (N)	6971	2241	83,389	6688	3875	143,249
Runners	62.56%	49.17%	84.36%	36.80%	34.76%	74.56%
Male	64.94%	67.16%	54.29%	59.09%	58.86%	46.97%
Prior MI	8.59%	15.66%	4.96%	16.61%	16.77%	0.79%
Preexisting diabetes	4.52%	5.58%	0.80%	8.88%	6.43%	0.99%
Preexisting hypertension	26.68%	34.09%	5.48%	37.57%	33.99%	5.76%
Age (years)	55.51±11.25	59.07±10.15	44.92±11.70	59.17±11.54	59.24±10.96	44.00±12.34
Follow-up (years)	6.35±1.69	5.94±1.37	6.92±1.77	10.07±2.53	9.68±2.01	11.65±3.15
Education (years)	16.29±2.67	16.16±2.84	16.28±2.46	15.61±2.85	15.68±2.82	15.99±2.58
Smokers	1.66%	1.65%	1.84%	3.35%	2.84%	2.80%
Red meat (servings/d)	0.38±0.36	0.38±0.36	0.36±0.36	0.38±0.36	0.38±0.36	0.36±0.41
Fruit (pieces/d)	1.65±1.19	1.69±1.24	1.58±1.14	1.60±1.26	1.61±1.22	1.52±1.22
Alcohol (g/d)	8.76±12.83	8.77±12.72	7.94±11.95	8.93±14.68	9.05±14.37	8.78±13.72
Aspirin (tablets/d)	0.47±0.71	0.57±0.67	0.27±0.61	0.57±0.74	0.56±0.72	0.26±0.60
BMI (kg/m^2)	25.17±3.96	25.86±3.99	23.31±3.33	26.67±4.77	26.53±4.42	23.79±3.98
Exercise (Metabolic equivalent-hours/d)	3.64±2.77	3.27±2.50	4.81±3.22	2.87±2.36	2.85±2.23	4.46±3.19

clinical trial. All participants of the National Runners' Health Study II and the National Walkers' Health Study were sent surveys, but recruitment ceased once 50,000 follow-up questionnaires were received. Baseline and follow-up questionnaires provided the subject's height, weight, exercise regimen, dietary practices, cigarette use, and prescribed medications. Smokers were defined as participants who reported smoking cigarettes at the time of their baseline survey. Aspirin use was reported as tablets/week without regard to dosage. The study protocol was approved by the University of California Berkeley Committee for the Protection of Human Subjects, and all subjects provided a signed statement of informed consent.

Metabolic equivalents of energy expenditure (METs) were determined as follows. Walking distance was converted into duration (i.e., distance/mph) and MET-h/d was calculated from the average hours walked per day and the MET value for the reported pace.[17] Running MET values were calculated as 1.02 MET-h/km.[18] In addition, exercise energy expenditure was determined as multiples of the current physical activity recommendations [23],[19] that is, inadequate exercise (<450 MET-min/wk or 1.07 MET-h/d), satisfying the recommendations (450 to 750 MET-min/wk or 1.07 to 1.8 MET-h/d), exceeding the recommendations by 1- to 2-fold (1.8 to 3.6 MET-h/d), and exceeding the recommendation by ≥2-fold (≥3.6 MET-h/d). Running and walking energy expenditures were combined to maximize statistical power.

For mortality surveillance, hypercholesterolemic patients were defined as patients who reported taking medications for high cholesterol on their baseline questionnaire. Fatal events were determined from the National Death Index, which provided both underlying and contributing causes of death (entity axis) by the *International Classification of Disease Ninth Revision* (before 1999, ICD9) and *Tenth Revision* (1999 to 2008, ICD10).[20] All CVD-related deaths were identified having entity axis code of ICD9-390.0 to 459.9 or an ICD10-I00 to I99, and all diabetes-related deaths were identified having entity axis code of death of ICD9-250 or an ICD10-E10.0 to 14.9 [17].[20] Cox proportional hazard analyses were used to assess the relation between distance ran or walked and mortality when adjusted for baseline gender; age (age and age^2); exercise mode (running vs walking); cohort (first or second recruitment); education; smoking status; intakes of meat, fruit, alcohol, and aspirin; previous MI; and baseline diabetes medication use.

For the follow-up survey of nonfatal events, hypercholesterolemic patients were defined by their baseline cholesterol medication use, or a physician diagnosis for high cholesterol before their baseline survey (obtained from their follow-up questionnaire). Three end points were examined: nonfatal CVD, nonfatal diabetes, and nonfatal hypertension. Nonfatal incident hypertension and diabetes were defined as initiating antihypertensive and antidiabetic medications or a physician diagnosis of hypertension since baseline on the participant's follow-up questionnaire. Nonfatal incident CVD was defined as the earliest incidence of angina, percutaneous coronary angioplasty, coronary artery bypass graft surgery, myocardial infarction (MI), or stroke. Self-reported hypertension and hypercholesterolemia have been demonstrated as consistent by repeated surveys and reliable as confirmed by medical records[21] and have been used by the Nurses' Health Study[22] and other major cohort studies.[23] Analyses of incident nonfatal CVD, diabetes, and hypertension excluded subjects with preexisting baseline CVD, diabetes, and hypertension, respectively. Cox proportional hazard analyses adjusted for baseline gender; age; exercise mode; cohort; education; smoking status; intakes of meat, fruit, alcohol, and aspirin. In addition, the analyses of incident diabetes were adjusted for previous MI, the analyses of incident CVD adjusted for baseline diabetes medication, and the analyses of hypertension adjusted for both previous MI and baseline diabetes medication.