Physical Exertion, Exercise, and Sudden Cardiac Death in Women

William Whang, MD, MS

JoAnn E. Manson, MD, DrPH

Frank B. Hu, MD, PhD

Claudia U. Chae, MD, MPH

Kathryn M. Rexrode, MD, MPH

Walter C. Willett, MD, DrPH

Meir J. Stampfer, MD, DrPH

Christine M. Albert, MD, MPH

R EGULAR EXERCISE HAS NUMER-ous cardiovascular benefits and has been associated with improved cardiovascular and all-cause mortality.[1-6] Current recommendations for healthy adults prescribe at least moderate-intensity physical activity for 30 minutes or longer almost daily.[7] However, as with any recommendation, individual physicians must weigh both the benefits and risks of exercise for individual patients.[8] Despite all of the known benefits of exercise, there are also well-documented associations between acute episodes of exertion and sudden cardiac death.[9-15] Although exertion-related sudden cardiac deaths are relatively rare compared with other health outcomes, these deaths commonly occur in an unexpected fashion among those who appear quite healthy,[16,17] and therefore, this risk remains troubling for both physicians and patients.

Among men, it has been estimated that approximately 6% to 17% of all sudden cardiac deaths occur in association with acute exertion,[9,10,12,13] and vigorous exertion has been demonstrated to simultaneously trigger[9,10] and protect[9,10,18-22] against sudden cardiac death. Prior epidemiological and autopsy studies[14,23,24] have suggested that

Context Exercise is associated with a lower risk of cardiovascular events but may transiently increase the risk of ventricular arrhythmias. Its short-term and long-term associations with risk of sudden cardiac death among women are unclear.

Objectives To compare the risk of sudden cardiac death in women during moderate to vigorous exertion with the risk of sudden cardiac death during lighter or no exertion; and to assess the long-term association between moderate to vigorous exercise and sudden cardiac death.

Design, Setting, and Participants Prospective, nested case-crossover study of 288 cases of sudden cardiac death within the Nurses' Health Study (1980-2004); and a prospective cohort analysis of 69 693 participants without prior cardiovascular disease followed up from 1986-2004.

Main Outcome Measure Risk of sudden cardiac death associated with moderate to vigorous exertion.

Results The absolute risk of sudden cardiac death associated with moderate to vigorous exertion was exceedingly low at 1 per 36.5 million hours of exertion. In case-crossover analyses, the risk of sudden cardiac death was transiently elevated during moderate to vigorous exertion (relative risk [RR], 2.38; 95% confidence interval [CI], 1.23-4.60; P=.01) compared with the risk during lesser or no exertion. Habitual moderate to vigorous exertion modified this transient risk (P=.005 for interaction) and the risk was no longer significantly elevated among those who exercised 2 or more hours per week. In the cohort analyses, an increasing amount of moderate to vigorous exercise was associated with a lower long-term risk of sudden cardiac death in age-adjusted and multivariable models that excluded biological intermediates (P=.006 for trend). This relationship was attenuated when biological intermediates were included (P=.06 for trend); however, the reduction in risk remained significant among women who exercised 4 or more hours per week (adjusted RR, 0.41; 95% CI, 0.20-0.83; P=.01) compared with women who did not exercise.

Conclusions These prospective data suggest that sudden cardiac death during exertion is an extremely rare event in women. Regular exercise may significantly minimize this small transient risk and may lower the overall long-term risk of sudden cardiac death.

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women may have a lower risk of exertion-related sudden cardiac death; however, to our knowledge, there has been no large-scale prospective assessment of this risk. The ongoing Nurses' Health Study, a cohort of 121 701 women who have been intensively followed up for up to 28 years, presented a unique opportunity to quantify the absolute and relative risk (RR) of exertion-related sudden cardiac death in women and to further define the possible role regu-

Author Affiliations: Cardiovascular Division, Massachusetts General Hospital, Boston (Drs Whang, Chae, and Albert); Channing Laboratory and the Department of Medicine, Harvard Medical School (Drs Manson, Hu, Willett, and Stampfer), Division of Preventive Medicine (Drs Manson, Chae, Rexrode, Stampfer, and Albert), and Center for Arrhythmia Prevention, Division of Preventive Medicine and Cardiovascular Division (Dr Albert), Brigham and Women's Hospital; and the Departments of Epidemiology (Drs Manson, Hu, Willett, and Stampfer) and Nutrition (Drs Willett and Stampfer), Harvard School of Public Health.
Corresponding Author: Christine M. Albert, MD, MPH, Center for Arrhythmia Prevention, Division of Preventive Medicine and Cardiovascular Division, Brigham and Women's Hospital, 900 Commonwealth Ave E, Boston, MA 02215 (calbert@partners.org).

lar exercise may play in predicting risk of sudden cardiac death.

METHODS
The Nurses' Health Study Cohort

The Nurses' Health Study began in 1976 when 121 701 female registered nurses, aged 30 to 55 years, completed a questionnaire about their medical history, coronary heart disease (CHD) risk factors, and lifestyle factors. The cohort has been followed up every 2 years with mailed questionnaires that update exposure information and inquire about newly diagnosed medical illnesses. Deaths are reported by next of kin or postal authorities or identified through the National Death Index. Family members are asked for permission to obtain further information from medical records and are interviewed about the circumstances surrounding the death if it was not adequately documented in the medical record. Subjects or family members provided written, informed consent, and the study was approved by the institutional review board of Partners HealthCare System, Boston, Mass.

Assessment of Habitual Physical Activity

In 1980, women were asked to report the average number of combined hours spent each week over the past year on moderate to vigorous activities such as digging in the garden, vigorous sports, jogging, brisk walking or striding, bicycling, yard work, and housework. Beginning in 1986, questionnaires inquired about the average amount of time spent briskly walking, jogging, running, bicycling, lap swimming, playing tennis or squash, or participating in aerobics or calisthenics per week during the past year. Information on other exertional activities was not collected on the 1986 or 1988 questionnaires. From 1992 onward, questionnaires asked about the average amount of time spent per week in the activities listed above, in lower-intensity exercise such as yoga, and in other exertional activities such as mowing the lawn. Re-

ported moderate to vigorous activity on this questionnaire has a correlation of 0.62 with reported exertion in 1-week activity diaries[25]; and the physical activity score from a similar questionnaire had a correlation of 0.54 with maximal oxygen consumption.[26]

Definition of Sudden Cardiac Death

The main study end point was sudden cardiac death occurring before June 1, 2004. The specific details regarding the classification of sudden cardiac death in this cohort are described in detail elsewhere.[17] Briefly, a cardiac death was considered sudden if the death or cardiac arrest that precipitated death occurred within 1 hour of symptom onset as documented by medical records or reports from next of kin. Unwitnessed deaths that could have occurred within 1 hour of symptom onset and that had autopsy findings consistent with sudden cardiac death (n=30; 10.4%) were considered probable sudden cardiac deaths and also were included in the analysis. Because the rigorous definition of sudden cardiac death used excludes most deaths during sleep (and some of these deaths may have been sudden), the systematic exclusion of these deaths in this analysis could bias our results toward a positive association. Therefore, we also performed sensitivity analyses including these deaths.

Assessment of Physical Activity at Time of Death

The specific activity that the participant was engaged in at the time of sudden cardiac death was ascertained from the medical record or reports from next of kin. The degree of physical exertion was then quantified on a scale of 1 to 8 metabolic equivalents (1 metabolic equivalent=3.5 mL/kg per minute of oxygen consumption), and the participant was considered exposed to moderate to vigorous exertion if the activity was estimated to be 5 or more metabolic equivalents.[27] If the activity was unknown (n=67; 23% of cases) or known to be less than 5 metabolic

equivalents, the participant was considered unexposed.

Statistical Analyses

Exertion Analyses. For the exertion analysis, 84 888 women provided information on hours per week of usual moderate to vigorous exertion at baseline in 1980. Information on exertion was then updated in 1992, 1996, 1998, and 2000. The absolute risk of exertion-related sudden cardiac death (ratio of exertion-related sudden cardiac deaths to the total hours of usual moderate to vigorous exertion in the cohort) was compared with the incidence of sudden cardiac death during lesser activity. The absolute risk difference also was calculated.

A nested case-crossover design was used to quantify the RR of sudden cardiac death during an episode of moderate to vigorous exertion compared with the risk during periods of lighter or no exertion.[28] In this type of analysis, the stratifying variable is the individual patient, as in a crossover experiment in which each individual serves as both a case and control (self-matching). For each case of sudden cardiac death, the ratio of the observed exposure to moderate to vigorous exertion at the time of the sudden cardiac death to that expected based on the usual amount of exertion reported on the most recent questionnaire was used to calculate an odds ratio as a measure of RR.[10,28] To assess modification of the RR by usual exertion, the analysis was then stratified by 2 categories of habitual exertion (<2 hours per week, ≥2 hours per week) and a χ^2 test for homogeneity was used to compare these estimates of RR. Because this design minimizes but does not completely exclude interindividual confounding, secondary analyses were performed that excluded women who developed CHD prior to their sudden cardiac death.

Exercise Analyses. For the exercise analyses, assessments of usual moderate to vigorous exercise were based on self-reported time spent per week walking or hiking outdoors at a pace of 3.0 mph or more, jogging, running, bicy-

cling, lap swimming, playing tennis or squash, participating in other aerobic exercise such as dance or using a stair machine, or participating in lower-intensity exercise such as yoga. Activities were reported on the 1986, 1988, 1992, 1996, 1998, and 2000 questionnaires. First, the case-crossover analysis was repeated, limiting the exposures to these activities. Second, to assess the overall long-term association between regular moderate to vigorous exercise and sudden cardiac death, a prospective cohort analysis was performed. Because the presence of prior disease may influence physical activity, women who had reported CHD, stroke, or cancer prior to 1986 were excluded, leaving 69 693 women aged 40 to 65 years with physical activity at baseline. Proportional hazards models were used to compute age-adjusted and multivariable-adjusted hazards ratios as estimates of RR across 4 categories of exercise. Exercise and other variables were updated as time-dependent variables according to the most recent questionnaire. Tests for linear trend were performed by assigning each observation the median value of its corresponding exercise category and by including this as a continuous variable in separate proportional hazards models. All reported P values are 2-sided. Statistical analysis was performed using SAS software version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

There were 288 sudden cardiac death cases among 84 888 women who responded to the 1980 questionnaire over 1.93 million person-years of follow-up. Of these, only 9 deaths (3.1%) occurred during an episode of moderate to vigorous exertion and only 3 of these occurred during activities that would be considered exercise. The specific activities were yard work (n=3), swimming (n=2), housework (n=2), physical therapy (n=1), and shoveling snow (n=1). The overall risk of sudden cardiac death associated with moderate to vigorous exertion was 1 per 36.5 million hours of risk

compared with an incidence of 1 sudden cardiac death per 59.4 million hours of activity with lesser exertion. Thus, the unadjusted excess risk was only 1 excess death per 94.7 million hours of exertion. The overall risk during moderate to vigorous exercise was similar to that during exertion at 1 per 41 million hours of risk.

Using the case-crossover method, the RR of sudden cardiac death during moderate to vigorous exertion was modestly elevated at 2.38 (95% confidence interval [CI], 1.23-4.60; P=.01) compared with risk at other time points. This transient elevation in risk was lower and no longer significant among women who reported 2 or more hours per week of moderate to vigorous exertion (RR, 1.49; 95% CI, 0.61-3.61)

compared with women who reported 2 or fewer hours per week of exertion (RR, 8.98; 95% CI, 3.32-24.30; P for interaction=.005). These results did not materially differ when unheralded deaths that occurred during sleep were included, if the exposure was limited to exercise, or if women with a prior history of CHD were excluded.

The relationship between habitual level of exercise and long-term risk of sudden cardiac death from 1986 to 2004 also was examined. Among 69 693 women without a history of CHD, stroke, or cancer at baseline, 22 172 (32%) reported no regular moderate to vigorous exercise and only 10 680 (15%) reported exercising 4 or more hours per week (TABLE 1). In age-adjusted analyses, amount of moderate to vigorous ex-

Table 1. Coronary Heart Disease Risk Factors Among Women Without Prior Coronary Heart Disease or Stroke by Usual Amount of Moderate to Vigorous Exercise*

	Moderate to Vigorous Exercise in 1986 by Hours/Week (N = 69 693)			
	0 (n = 22 172)	>0-1.9 (n = 26 089)	2-3.9 (n = 10 752)	≥4 (n = 10 680)
Age, mean (SD), y†	53.0 (7.06)	52.3 (7.13)	52.1 (7.09)	52.6 (7.15)
Smoking† Past	6549 (29.5)	8867 (34.0)	4245 (39.5)	4261 (39.9)
Current, No. of cigarettes/d 1-14	1606 (7.2)	1665 (6.4)	683 (6.4)	687 (6.4)
15-24	2442 (11.0)	2093 (8.0)	638 (5.9)	638 (6.0)
≥25	2161 (9.8)	1392 (5.3)	339 (3.2)	347 (3.3)
Reported diagnosis Diabetes†	944 (4.3)	861 (3.3)	274 (2.6)	235 (2.2)
High cholesterol‡	2575 (11.6)	3048 (11.7)	1190 (11.1)	1162 (10.9)
Hypertension†	5941 (26.8)	6076 (23.3)	2238 (20.8)	2145 (20.1)
Body mass index ≥30†§	4494 (20.3)	3578 (13.7)	938 (8.7)	714 (6.7)
Parental history of MI prior to age 60 y	3027 (13.7)	3621 (13.9)	1475 (13.7)	1412 (13.2)
Alcohol intake, g/d† 0.1-4.9	5858 (26.4)	7821 (30.0)	3320 (30.9)	3138 (29.4)
5.0-14.9	3313 (14.9)	4814 (18.5)	2163 (20.1)	2278 (21.3)
≥15.0	2187 (9.9)	2612 (10.0)	1180 (11.0)	1357 (12.7)
Aspirin use ≥7/wk†	4048 (18.3)	4445 (17.0)	1707 (15.9)	1651 (15.5)
Postmenopausal†	12 778 (57.6)	13 898 (53.3)	5581 (51.9)	5915 (55.4)
Energy intake, mean (SD), %† ω-3 Fatty acid	0.11 (0.09)	0.12 (0.10)	0.14 (0.11)	0.15 (0.12)
α-Linolenic acid	0.57 (0.15)	0.57 (0.15)	0.57 (0.15)	0.57 (0.15)
Supplement use† Vitamin E	2431 (11.0)	3882 (14.9)	1851 (17.2)	1928 (18.1)
Multivitamin	7262 (32.8)	10 390 (39.8)	4488 (41.7)	4659 (43.6)

Abbreviation: MI, myocardial infarction.
*Coronary heart disease risk factors are standardized for age to the total cohort. Values are expressed as number (percentage) unless otherwise indicated.
†P<.01 for trend across excercise categories.
‡P<.05 for trend across exercise categories.
§Calculated as weight in kilograms divided by the square of height in meters.

Table 2. Long-term Mortality Risk Among Women by Moderate to Vigorous Exercise for 1986-2004

	HR (95% CI) of Mortality by Hours/Week of Moderate to Vigorous Exercise for 1986-2004 (N = 69 693)*				
	0 (n = 394 645)	>0-1.9 (n = 410 927)	2-3.9 (n = 189 377)	≥4 (n = 203 798)	P for Trend
Sudden cardiac death					
No. of cases	74	46	28	9	
Age-adjusted	1.00	0.66 (0.46-0.96)	0.91 (0.59-1.40)	0.27 (0.14-0.54)	.001
Multivariable 1†	1.00	0.79 (0.54-1.15)	1.28 (0.82-2.01)	0.41 (0.20-0.83)	.06
Multivariable 2‡	1.00	0.73 (0.51-1.07)	1.08 (0.69-1.68)	0.32 (0.16-0.64)	.006
All-cause mortality					
No. of cases	3122	1877	620	580	
Age-adjusted	1.00	0.66 (0.62-0.70)	0.48 (0.44-0.53)	0.41 (0.38-0.45)	<.001
Multivariable 1†	1.00	0.73 (0.69-0.78)	0.60 (0.55-0.65)	0.51 (0.47-0.56)	<.001
Multivariable 2‡	1.00	0.72 (0.68-0.76)	0.58 (0.53-0.63)	0.50 (0.45-0.54)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio,
*The HRs are from proportional hazards models with time-dependent variables and were used to estimate relative risk.
†Adjusted for age, smoking status (never, past, current smoking [1-14 cigarettes/d, 15-24 cigarettes/d, ≥25 cigarettes/d), body mass index (calculated as weight in kilograms divided by the square of height in meters; <25, 25-29.9, ≥30), alcohol intake (0 g/d, <5 g/d, 5-14 g/d, ≥15 g/d), menopausal status and postmenopausal hormone use, usual aspirin use (<1/wk, 1-6/wk, and ≥7/wk), multivitamin use (yes vs no), vitamin E supplement use (yes vs no), history of hypertension (yes vs no), hypercholesterolemia (yes vs no), diabetes (yes vs no), family history of myocardial infarction (no or yes [age <60 years or >60 years]), history of coronary heart disease, history of stroke, ω-3 fatty acid intake (quintiles), α-linolenic acid intake (quintiles).
‡Adjusted for factors in multivariable 1, except for likely causal biological intermediates (hypertension, hypercholesterolemia, diabetes, body mass index, coronary heart disease).

ercise was inversely related to sudden cardiac death risk (**TABLE 2**). After controlling for age, smoking status (never, past, current smoking [1-14 cigarettes/d, 15-24 cigarettes/d, ≥25 cigarettes/d), body mass index (calculated as weight in kilograms divided by the square of height in meters; <25, 25-29.9, ≥30), alcohol intake (0 g/d, <5 g/d, 5-14 g/d, ≥15 g/d), menopausal status and postmenopausal hormone use, usual aspirin use (<1/wk, 1-6/wk, ≥7/wk), multivitamin use (yes vs no), vitamin E supplement use (yes vs no), history of hypertension (yes vs no), hypercholesterolemia (yes vs no), diabetes (yes vs no), family history of myocardial infarction (no, yes [age <60 years, age ≥60 years]), history of CHD, history of stroke, ω-3 fatty acid intake (quintiles), and α-linolenic acid intake (quintiles), the inverse relationship between amount of moderate to vigorous exercise and sudden cardiac death risk was attenuated; however, a trend persisted (P=.06 for trend). If plausible biological intermediates (hypertension, diabetes, body mass index, hypercholesterolemia, and CHD) that existed or occurred prior to sudden cardiac death were excluded from the model, the

inverse relationship was again statistically significant (P=.006 for trend). The reduction in sudden cardiac death risk was observed primarily among women who exercised 4 or more hours per week (RR, 0.41; 95% CI, 0.20-0.83; P=.01 in the fully adjusted model). Again, these results were similar when unheralded deaths that occurred during sleep were included as sudden cardiac deaths. Using similar multivariable models, all-cause mortality also was inversely associated with greater amounts of exercise (Table 2; P<.001 for trend). Similar results for all-cause mortality were noted when the first 4 years of follow-up were excluded as a way of reducing the risk of reverse causality.

COMMENT

In this large prospective cohort of women, the absolute risk of exertion-related sudden cardiac death was exceedingly low (1 per 36 million hours of risk). Although there was a transient elevation in risk associated with exertion, this elevation was modest and was limited to the less habitually active women. In addition, the overall long-term risk of sudden cardiac death tended to be lower among women who partici-

pated in greater amounts of moderate to vigorous exercise, particularly among those who exercised 4 or more hours per week in which the risk reduction was significant. Consistent with prior reports on the Nurses' Health Study cohort, total mortality was significantly lower among women who exercised regularly.[5]

To our knowledge, this analysis is the first to prospectively assess both the transient and long-term risk of sudden cardiac death associated with physical activity among women. Although our data are consistent with prior analyses in men that suggest that physical exertion may trigger sudden cardiac death and that habitual exercise diminishes this risk,[9,10] the magnitude of the risk is much lower in this cohort of women compared with a similar cohort of men[10] in which the risk was 1 sudden cardiac death per 1.51 million episodes of vigorous exertion. Despite lower baseline absolute risks of sudden cardiac death in these women, the RR during an episode of vigorous exertion was approximately 19-fold higher (RR, 44.9; 95% CI, 26.7-75.4) among men enrolled in the Physicians' Health Study[10] than that observed during an episode of moderate to vigorous exertion in the Nurses' Health Study cohort (RR, 2.38; 95% CI, 1.23-4.60). Part of this difference could be due to the inclusion of moderate exertion in our exercise measure. However, a similar sex difference was observed in smaller retrospective studies in Finland[14] and in the United States[24] where the same measures of exercise yielded a 9-fold to 14-fold higher risk of exertion-related sudden cardiac death among men.

There are several limitations to our study. Our study cannot prove causality, and the association between exercise and sudden cardiac death could at least in part be due to residual confounding. This is particularly true for the total mortality result in which prior analyses in this cohort demonstrated that part of this association is likely due to reverse causation (ill health leads to sedentary behavior). Because the majority of women who experience a sudden cardiac death were previously healthy, the

bias of reverse causation is less problematic for the primary sudden cardiac death analysis. Although we attempted to update physical activity as frequently as possible, there is still the chance for misclassification between questionnaire years. If such misclassification were random, then our results would be biased toward attenuating the association between physical activity and sudden cardiac death. Finally, although this is the largest prospective study of exertion-related sudden cardiac death in women, the rarity of this event and the resultant small number of exertion-related sudden cardiac deaths in the case-crossover analyses limits the precision of our estimates.

In summary, sudden cardiac death during exertion is an extremely rare event in women, and exercising regularly can significantly minimize risk. Therefore, these data should provide reassurance that moderate to vigorous levels of exercise can be prescribed in a safe fashion to women, and if performed regularly, exercise may even lower long-term risk of sudden cardiac death.

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