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A MODEL FOR DEFINING THE OPTIMAL AMOUNT OF EXERCISE CONTRIBUTING TO HEALTH AND AVOIDING SUDDEN CARDIAC DEATH

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Abstract

Background and Aims: Sudden cardiac death is the first symptom of heart disease in 25 to 40% of people. This paper introduced a model that can help determine the optimum amount of exercise in relation to a categorical outcome variable such as sudden death, stroke, inflammation or infection.

Methods: We illustrated its utility using data from the Physicians' Health Study to predict the optimal exercise patterns that protect people from coronary artery disease while minimizing the risk of sudden cardiac death during exercise. The model extended the utility of case-crossover methods, which yield an odds ratio of dying while exercising compared to rest.

Results: With the assumption that the relative frequency of sudden death during exercise is linearly related to the proportion of time spent exercising, the analysis rendered a "U-shaped" curve between the relative risk of sudden death and the weekly volume of moderate intensity exercise. The model predicted that men 40 to 80 yr should exercise 30 minutes a day (≥ 6 METS) six days a week to receive the benefits of exercise and minimize the risk of sudden death.

Conclusions: These results were consistent with exercise recommendations from the American College of Sports Medicine and the American Heart Association.

Lower or higher amounts of exercise increased the risk of sudden death. Exercise is extremely safe in the absence of heart disease. Heart disease often has no symptoms, so people have no way of knowing definitively if they are in the high-risk cohort. This model is useful for other "U" shaped phenomena, such as exercise induced inflammation, stroke, and upper respiratory infection.

Key words: *exercise, sudden death, heart, coronary artery disease, sport, epidemiology*

Introduction

Throughout history medical experts have vacillated over the relative risks and benefits of sport and exercise. Ancient physicians, such as Hippocrates and Galen, warned against the health risks of excessive exercise and athletic participation (1). As recently as the 1970's, some medical experts questioned whether the benefits of exercise compensated for the increased risk of sudden death (2).

Conversely, others called endurance exercise an *elixir vitae* that conferred immunity from coronary heart disease. The Bassler hypothesis, for example, formulated in the 1970's, suggested that marathon running provides immunity against coronary artery disease and fatal myocardial infarction. The hypothesis was based on the observation that marathon runners did not appear to get coronary artery disease (3). More than 30 years of systematic observations of endurance athletes, however, have not supported this hypothesis (4).

Lack of physical activity or low levels of physical fitness are risk factors of coronary artery disease (CAD), stroke, and upper respiratory infections (5). Regular physical activity is considered healthful, but excessive exercise may be less beneficial or even harmful. Moderate amounts of exercise reduce the risk of sudden death, stroke, upper respiratory infection, and markers of inflammation (5). These benefits decrease or disappear as the volume of exercise increases. A "U" or "J-shaped" curve describes the relationship between the volume of exercise and its effects on health. Beyond optimal levels greater amounts of exercise are less beneficial or even harmful. A model might be useful for predicting the optimal amount of exercise that approximates the nadir of the "U- or J shaped" curves and renders the optimal risk-benefit ratio.

This paper introduced a model that can help determine the optimum amount of exercise in relation to a categorical outcome variable such as sudden death, stroke, inflammation or infection. We illustrated the utility of the model by predicting optimal exercise patterns that protect people from coronary artery disease while minimizing the risk of sudden death during exercise.

Regular physical activity reduces the risk of CAD in most people. However, exercise also stresses the heart and can trigger sudden cardiac death (6). Physical inactivity increases the risk of CAD but poses a minimal exposure to exercise-induced sudden death. In contrast, habitual physical activity reduces the risk of CAD but increases exposure to sudden cardiac death. These observations suggest that there might be an optimal level of habitual physical activity— one that enhances the protective effects of exercise and minimizes the risk of exercise-triggered sudden cardiac death.

The Physicians Health Study followed 21,481 physicians— age 40-84 yr— for 12-yr (7). Part of the study compared the risk of sudden death during exercise with that occurring at rest or low-levels of exertion. The study also examined the relationship between vigorous exercise and the overall risk of death from CAD. These data present an excellent opportunity to identify the optimal activity levels that will reduce the risk of CAD while minimizing the risk of exercise-induced sudden death. Our model extended case-crossover methods (8) to predict the optimal volume of exercise.

Materials and methods

The 12-yr Physicians' Health Study found 122 sudden deaths among the 21,481 male physicians (7). The subjects were free from cardiovascular disease at the beginning of the study. In their analysis of the data from the Physicians' Health Study, Albert, et al. (7) used the nested case-crossover design (8) to quantify the relative risk of sudden death from cardiac causes during or shortly after vigorous exercise. Exercise related sudden death was identified when subjects exercised at an intensity of ≥6 METS and died during or within 30 minutes of exercise. We included the post exercise period because it is associated with an increased risk of sudden death (4) . The incidence of death during and shortly after exercise was compared to deaths reported in subjects who were at rest or were doing low exertion activities. Sudden death was defined as death within one hour after the onset of symptoms or death after a witnessed cardiac arrest or abrupt collapse that was not preceded by symptoms lasting more than one-hour (7).

The data of Albert, *et al.* showed a relative risk of about 74 for men who engaged in habitual vigorous exercise less than one time per week, a relative risk of about 19 for men who exercised one to four times per week, and a relative risk of about 11 for men who exercised five or more times per week. Extrapolating from these results suggests there might be a minimum risk and an optimal exercise volume (9).

We shall explore this by first developing a model that extends case-crossover methods. The case-crossover approach lays out a contingency table in terms of person hours for each subject who dies. We shall use an example of a person who exercised 6 days a week for an hour per day of exposure to exercise-related sudden death trigger (30 minutes of exercise plus 30 minutes post exercise).

For the case of a person with sudden death during the higher-risk exercise period:

	Sudden Deaths	Non Sudden Deaths	Person-Hours
Exercise	1	5	6
Non exercise	0	162	162
			168

There were 168 person hours in a week. For seven such people (for example), each entry in the table was multiplied by seven.

Similarly, for each person who died suddenly but not during exercise, we can lay out a table:

	Sudden Deaths	Non Sudden Deaths	Person-Hours
Exercise	0	6	6
Non exercise	1	161	162
			168

For sixteen such people, for example, each entry in the table was multiplied by sixteen. Combining these contingency tables using Mantel Haenszel weighting methods (10) yielded an odds ratio of dying while exercising compared to dying at rest. For this example,

$$OR = 1x162x7/(1x6x16) \qquad (1)$$

Now, we can generalize this procedure. Let F_x, be the fraction of sudden deaths that occurred during exercise and P_x the proportion of time (i.e., one week) that exercise could trigger sudden death. Then:

$$OR =[F_x/ (1-F_x)] \quad [(1-P_x)/P_x] \qquad (2)$$

The data from Table 2 in the Albert, *et al.* (7) paper can be used to estimate a relationship between F_x, the fraction of deaths occurring in exercise and P_x, and the frequency of habitual vigorous exercise activity. Following the approach of Kessler (11), a linear relationship was derived using regression methods. Therefore, let:

$$F_x = \alpha + \beta P_x \qquad (3)$$

Combining equations 2 and 3 and taking the partial derivative with respect to P_x and setting the result equal zero yields the optimal value for P_x. This results in quadratic equation,

$$\beta(\beta-1) P_x^2 + 2\alpha\beta P_x + \alpha(\alpha-1) = 0 \qquad (4)$$

Equation 2 and 3 yield an odds ratio as a function of P_x, while equation 4 yields the optimal P_x, which minimizes the relative risk (odds ratio) (See Table 1).

Table 1. *The Effects of Exercise on the Odds Ratio of Sudden Death*

Sessions/wk	Time /Session	P_x	F_x	OR
0.5	0.25	0.00223	0.102	50.6
1	0.5	0.00595	0.125	23.9
2	0.5	0.0119	0.163	16.1
3	0.5	0.0179	0.200	13.8
4	0.5	0.0238	0.238	12.8
5	0.5	0.0298	0.275	12.4
6	0.5	0.0357	0.313	12.3
7	0.5	0.0417	0.350	12.4
7	0.75	0.0521	0.416	13.0
7	1.0	0.0625	0.482	13.9
7	1.25	0.0729	0.548	15.4
7	1.5	0.0833	0.613	17.4
7	1.75	0.0938	0.679	20.4
7	2.0	0.104	0.745	25.1
7	2.25	0.115	0.810	33.0
7	2.5	0.125	0.876	49.5

Note: time/session is in hours; P_x includes exercise time plus 30 minutes of post exercise time per session. OR =[F_x/ (1-F_x)] [(1-P_x)/P_x] with F_x = α + β. For the Albert et al. data, F_x = .0876 + 6.31 P_x, r = 0.99 (15). The optimal P_x is the solution of the quadratic equation $\beta(\beta-1) P_x^2 + 2\alpha\beta P_x + \alpha(\alpha-1) = 0$, with the optimal P_x = 0.035 for the Physicians' Health Study data (7).

We demonstrated the utility of this model using sudden death as the criterion variable. However, the model could be applied to any categorical outcome variable, such as all-cause mortality, stroke, inflammation, or infection.

Results

The model estimated the optimal amount of exercise that is protective while minimizing the risk of sudden death. The optimal solution minimizes the relative risk (odds ratio) of sudden death during vigorous exercise exposure as compared to light or no exercise. Note (Fig. 1) the optimum proportion of time exercising (P_x) is reasonably broad between 0.02 and 0.05 with a distinct minimum risk of about 0.035.

The model predicted that the optimal amount of vigorous exercise (6 METS or more) is 30 minutes a day, six days a week (5443 kJ/wk), with a range of 4 to 7 days per week (3600 to 6364 kJ/wk). Physical inactivity or exercising below the 6 MET threshold led to an increased relative risk. Exercising vigorously 7 days a week for 2.5 hr per day also led to an increased relative risk. Based on this model analysis, sedentary people might be advised to start a gradual exercise program, while over-active people might be advised to cut back on the volume of exercise in their program.

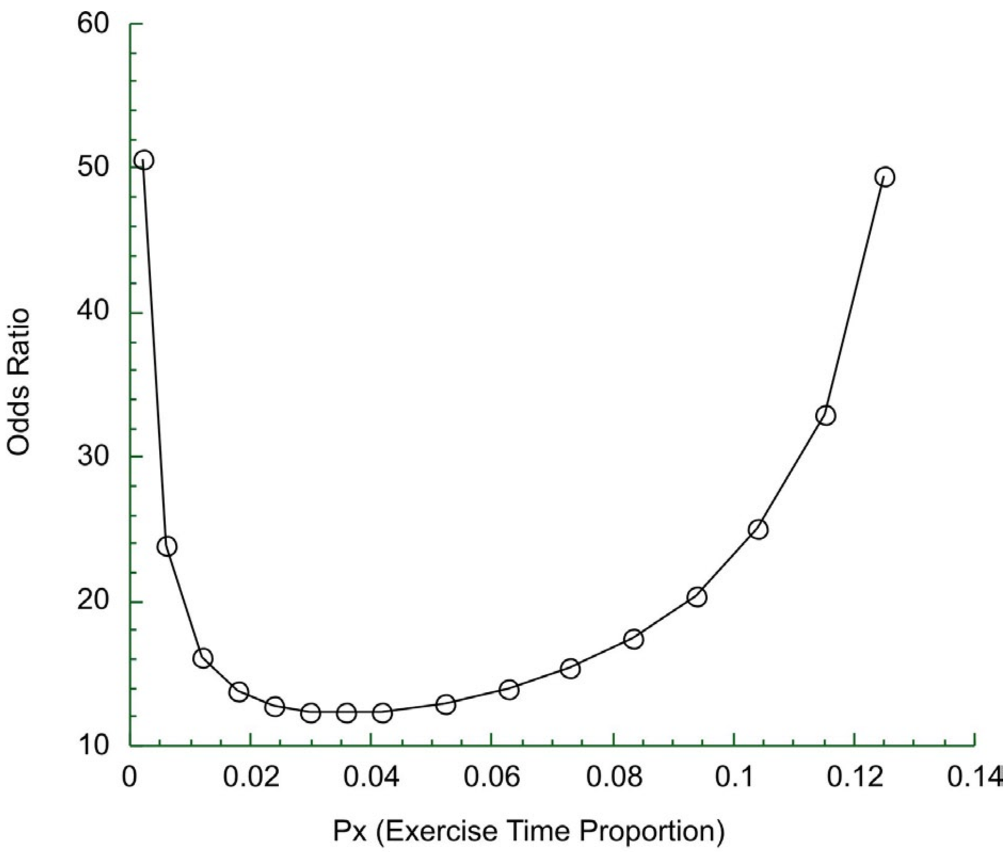

Fig. 1. *Odds ratio of sudden death in vigorous exercise versus light exercise or none, calculated from the data of Albert, et al. (7) using equations 2 and 3*

Discussion

The model analysis of the data from the Physicians' Health Study showed that men 40 to 80 yr can get the health benefits from exercise and minimize the risk of sudden death by exercising at a moderate intensity 30 minutes a day, six days a week. This finding is consistent with the exercise recommendations from the American College of Sports Medicine and the American Heart Association (5). The recommendations were based on a large body of scientific studies showing that regular, moderate intensity exercise dramatically reduces the risk of many diseases and health problems. The report highlighted the large body of research on exercise, disease, and longevity published during the past 30 years. It summarized two findings that are particularly significant to the average person: (1) Regular physical activity may be the single most important health practice for promoting wellness, and (2) moderate intensity exercise is sufficient to get most of the benefits. Our current model study reinforces an important theme of the report that regular moderate intensity exercise is an important health habit.

The relative risk of sudden death and physical activity followed a "U-shaped" curve. The model suggests that extreme exercise or a sedentary lifestyle may present a similar risk of sudden death. During extreme exercise sympathetic surges associated with acute exertion may promote plaque rupture (12). Furthermore, overtraining is associated with depressed immunity, insulin resistance, corticosteroid abnormalities, chronic fatigue, and depression, which might promote CAD and sudden death (13).

Is the risk of sudden death during exercise significant enough to cause concern? The incidence of sudden cardiac death during exercise is in the range of 1: 15,000 joggers per year (14). The data of Siscovick, *et al.* (15) showed 1 death per 17,000 (5.9/100,000) in men who did 1 to 19 min/week in vigorous activity; 1 death in 23,000 (4.3/100,000) for men who did 20 to 139 min/week; and 1 death per 13,000 (7.7/100,000) men who did more than 140 min/week. These data suggest that while sudden death is rare during exercise, its risk increases as a function of exercise duration. The subjects studied by Alpert, *et al.*— men between 40-80 yr— are more prone to sudden death at rest and during exercise compared to younger men, and there is no foolproof method for determining who will be in the cohort and who will not be. The risk of sudden death in the Alpert, *et al.* study— according to our model—increased alarmingly at the extreme ends of the exercise spectrum. So, the problem is worthy of continued analysis.

These data support a conclusion that both the relative risk (our model) and the absolute risk follow a "J" shape curve. The advantage of our modeling approach is that it allows us to interpolate among sparse data and predict an optimal exercise level. The present model accounts for the large and easily accessible health benefits of exercise while minimizing a very low absolute risk of sudden death during exercise.

The optimal exercise levels predicted from our model used the data from the Physician's Health Study. Therefore, the results are only applicable to middle aged and older men. Coronary artery disease is the leading cause of sudden death in this population (5). Congenital diseases, such as hypertrophic cardiomyopathy, are a more common cause of sudden death in younger men (6). Other causes of sudden cardiac death in young people include coronary artery anomalies, myocarditis, ruptured aortic aneurysms associated with Marfan's syndrome, aortic stenosis, arrhythmias, myocarditis, and commotio cordis (2).

The Physicians' Health Study attempted to examine the effects of intense exercise on sudden death. By necessity, any study that used such a large sample would be limited by relatively primitive measuring tools. Subjects were asked: "How often do you exercise vigorously enough to work up a sweat?" The possible responses were rarely or never, one to three times a month, once a week, two to four times a week, five or six times a week, or daily (7).

These data shed little light on the effects of intense exercise that might be practiced by masters level athletes. However, there is some evidence that older athletes who habitually exercise at maximum rates have a greater incidence of arrhythmias and, perhaps, an increased risk of sudden death during exercise (16).

Albert, *et al.* (7) showed that men who exercised vigorously less than once a week had a relative risk of sudden death during or shortly after exercise of 74 compared to 11 in men who exercised more frequently. Exercise training increases the ventricular fibrillation threshold (17), which reduces the risk of high intensity exercise. Also, sudden death may be linked with endothelial inflammation (18). Moderate exercise decreases markers of inflammation, such as C-reactive protein, while excessive exercise increases them (19). Seigal and co-workers (20) found at least a twofold increase in C-reactive protein, von Willebrand factor, D-dimer, WBC counts, and fibrinolytic activity in middle-aged men within 4 hours of running a marathon. Conversely, Geffken, *et al.* (19) found a decrease in C-reactive protein with moderate exercise. These findings reinforce the importance of moderation in the fitness program. People should avoid doing too little or too much exercise.

The relative risk of sudden death during exercise increases for younger people because their absolute risk at rest is lower than for older people (21). Therefore, increasing the volume of habitual exercise may contribute to a higher relative risk by increasing the absolute risk of sudden death during exercise, while lowering the absolute risk of sudden death at rest. Our analysis compared the risk of sudden death during exercise with the risk of sudden death at rest, which would therefore include the increased risk during exercise and the decreased risk at rest.

The proposed model might help predict the optimal amount of exercise for minimizing the risk of stroke and upper respiratory infection. Neiman (22) demonstrated a “J-shaped” curve between training volume and upper respiratory infection rates— moderate amounts decreased the risk, while high volume exercise (i.e., marathon running) increased the risk. Lee and Paffenbarger (23) demonstrated a similar relationship with stroke and energy expenditure (kJ/wk) from exercise. While stroke risk decreased with any amount of activity that exceeded 4187 kJ/wk, the relative risk (RR) was lower for subjects who expended 8374-12556 kJ/wk (RR=0.54) than for those who did no exercise (RR=1.0) or subjects who expended more than 16747 kJ/wk (RR=0.82).

In summary, this paper introduced a model that can help determine the optimal amount of exercise in relation to a categorical outcome variable such as sudden death, stroke, inflammation or upper respiratory infection. In applying the model to minimizing the risk of sudden death during physical activity, the results suggested that optimal amount of vigorous exercise is 30 minutes a day, six days a week at an intensity of at least 6 METS. These results agree favorably with current exercise recommendations from several professional organizations.

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