Physical activity, immobilization and the risk of venous thrombosis
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Chapter 4

The relationship between exercise and risk of venous thrombosis in elderly people

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Abstract

Objectives: To study whether exercise is associated with the risk of venous thrombosis in elderly people.

Design: Observational study with a median follow-up of 11.6 years.

Setting: The Cardiovascular Health Study in four U.S. communities.

Participants: People aged 65 and older without prior venous thrombosis (deep venous thrombosis or pulmonary embolism).

Measurements: Self-reported exercise was measured two or three times during follow-up and was defined as expending more than 500 kcal/wk on exercise, including walking for exercise. Venous thrombosis cases were verified using medical record review.

Results: Out of 5534 participants 171 developed a first venous thrombosis. Self-reported exercise at baseline was not related to the risk of venous thrombosis after adjustment for sex, age, race, self-reported health, and body mass index (adjusted hazard ratio (HR_{adj})=1.16, 95% confidence interval (CI)=0.84–1.61), although with exercise modeled as a time-varying exposure, overall results were in the direction of greater risk of venous thrombosis (HR_{adj}=1.38, 95% CI=0.99–1.91). For mild-intensity exercise, such as walking, there was a nonsignificant finding in the direction of benefit (HR_{adj}=0.75, 95% CI=0.49–1.16), but strenuous exercise, such as jogging, was associated with greater risk of venous thrombosis (HR_{adj}=1.75, 95% CI=1.08–2.83) than no exercise at all.

Conclusion: In elderly people, strenuous exercise was associated with a higher risk of venous thrombosis than no exercise at all. Future studies are needed to explain this unexpected higher risk.

Introduction

The incidence of venous thrombosis is 1 to 3 per 1,000 individuals per year. Rates increase with age, and the incidence is as high as 10 per 1,000 per year in elderly people.[1,2] Virchow postulated in 1856 that stasis of the blood was a major contributor to venous thrombosis,[3] and risks are greater in people who are temporarily immobilized or physically restrained.[4,5] For this reason, physical exercise might be expected to lower the risk of venous thrombosis, but little information is available about the association of exercise and venous thrombosis risk.

The Longitudinal Investigation of Thromboembolism Etiology (LITE) study combined data from two large cohort studies (the Cardiovascular Health Study (CHS) and the Atherosclerosis Risk In Communities (ARIC) Study) to investigate risk factors for venous thrombosis in people aged 45 to 100. Previously, an analysis in both cohorts reported no association to a slightly greater risk when studying leisure time physical activity and the risk of venous thrombosis.[6] In the Physicians' Health Study, exercise measured at baseline was associated with greater risk of venous thrombosis during the subsequent 21 years of follow-up.[7] By contrast, in a large population-based case-control study from the Netherlands (the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) Study) of participants aged 18 to 70, moderate and strenuous exercise were associated with lower risk of venous thrombosis in the upper[8] and lower extremities[9] than no exercise. Associations were similar in participants aged 60 and older and those younger than 60. A second case-control study in women aged 15 to 44 who were members of the Kaiser Permanente Medical Care Program also showed that vigorous-intensity exercise resulted in a risk of venous thrombosis of up to 50% less than no physical activity.[10]

Because the results from these observational studies regarding exercise and the risk of venous thrombosis are inconsistent, more information is needed. Neither the CHS nor the Physicians' Health Study analysis provided a detailed analysis of exercise with careful consideration of confounding and time-varying exercise exposure. To study further whether exercise is associated with the risk of venous thrombosis in elderly people, a detailed analysis was conducted in CHS with 4.5 additional years of follow-up and thus more thrombotic events than in the earlier analysis.[6] The analysis included careful consideration of confounding factors, updated assessment of exercise over time, and consideration of exercise intensity.

Methods

Study Population

During a 12-month period beginning in June 1989, four CHS field centers—located in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania—recruited a total of 5,201 participants who were aged 65 and older (original cohort). A supplemental minority cohort of 687 African-American participants was recruited in 1992 and 1993 from all CHS communities except Washington County. Each community sample was randomly obtained from the Medicare eligibility lists of the Health Care Financing Administration. Participants were considered eligible for participation whether or not they had a history of cardiovascular disease, but persons who were wheelchair bound or were receiving hospice treatment or radiation therapy or chemotherapy for cancer were excluded. Details of the CHS design and recruitment have been described elsewhere.[11] Of the persons contacted and eligible, 58% were enrolled in the study. Information regarding venous thrombotic events, death, and loss to follow-up were complete through December 2001.[2] Participants with self-reported venous thrombosis before baseline (n=354) were excluded from the present analyses. Institutional review boards at all study centers approved the study protocol, and informed consent was obtained from all participants.

Case Ascertainment

The CHS follow-up involved alternating telephone calls and clinic visits every 6 months. Hospitalizations were identified primarily according to self-report of the participant or proxy and search of Health Care Financing Administration records. For every hospitalization, hospital discharge summaries and *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) discharge codes were obtained. As previously published,[2] the CHS coordinating center identified cases of possible venous thrombosis events using the ICD-9-CM and procedure codes. Two physicians separately reviewed hospital records and assigned a venous thrombosis classification. Definite deep vein thrombosis required a positive duplex ultrasound, venogram, or other diagnostic test such as computed tomography. Probable deep vein thrombosis required a positive Doppler ultrasound or impedance plethysmography. Definite pulmonary embolism was based on high-probability ventilation–perfusion imaging classified according to Prospective Investigation of Pulmonary Embolism Diagnosis Study criteria, pulmonary angiogram, computed tomography, or autopsy. Probable and definite venous thrombosis and definite pulmonary embolism were considered together for analysis.[2,6]

Table 1. Prevalence of Various Characteristics by Exercise Status in 5534 Participants

	Sports exercise (>=500 kcal/week) N=2081		No Sports Exercise (<500 kcal /week) N=3453	
	N	%	N	%
Age				
65-69	791	38.0	1144	33.1
70-74	685	32.9	1067	30.9
75-79	386	18.6	738	21.4
80-84	156	7.5	360	10.4
85+	63	3.0	144	4.2
Female, %	984	47.3	2174	63.0
Black, %	221	10.6	656	19.0
Body mass index*				
<25	871	41.9	1287	37.4
25-30	906	43.7	1387	40.3
>= 30	298	14.4	767	22.3
Self-reported health*				
Excellent	382	18.4	386	11.2
Very Good	589	28.4	747	21.7
Good	755	36.3	1300	37.7
Fair	316	15.2	839	24.4
Poor	35	1.7	172	5.0
Education*				
< High school	469	22.6	1147	33.3
High school	557	26.8	966	28.1
> High school	1049	50.6	1329	38.6
Income*				
<$16000	628	32.7	1521	46.7
$16000-$25000	404	21.1	619	19.1
>$25000	887	46.2	1114	34.2
ADL, no impairment*	1995	96.0	3111	90.2
IADL, no impairment*	1736	83.6	2419	70.2
Weight change >4.5 kg in the preceding year				
Loss	236	12.0	447	13.7
Gain	136	6.9	333	10.2
Loss & Gain	118	6.0	243	7.4
No change	1484	75.1	2251	68.9

ADL= activities of daily living; IADL instrumental activities of daily living
* Information was missing regarding body mass index for 18; self-reported health 13, education 17, income 361, ADL 9, IADL 7 and weight change for 295 participants.

Each case was classified as idiopathic or secondary venous thrombosis. An event was considered secondary when it occurred within 90 days after acute medical conditions such as major trauma, surgery, or marked immobility or when it was related to cancer. All other venous thrombotic events were considered idiopathic. Venous thrombotic events that occurred within 12 months before or after a cancer diagnosis were considered to be related to cancer.[2]

Exercise Classification

A trained interviewer assessed exercise, race, self-reported health, weight change, activities of daily living (ADLs) and instrumental activities of daily living (IADLs) during the preceding year, and history of cardiovascular disease or cancer, and weight and standing height were measured.[11] ADLs characterize a person's ability to perform basic self-care activities, and IADLs characterize activities necessary for independent functioning in the community, such as housework and shopping.[12] Questionnaires regarding physical activities were administered at baseline (both cohorts), after 3 years of follow-up (original cohort), after 4 years of follow-up (minority cohort), and after 7 years of follow-up (original cohort).

At each exercise assessment, participants were asked to state which physical activities they had performed in the preceding 2 weeks and to indicate the number of times and duration of exercise in the preceding 2 weeks and the number of months per year that each activity was performed. They were specifically asked about walking for exercise, moderately strenuous household chores, mowing, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, calisthenics, and swimming. Participants could report two additional types of leisure time activities in two open text fields. For walking, the usual pace was asked (strolling, normal, fairly brisk, or brisk). In the present analysis, only sports activities, such as water aerobics, biking, jogging, rowing, and walking for exercise, were included; chores, work activities, and hobbies were excluded.

Average kilocalorie expenditure per week was calculated by multiplying the metabolic equivalent (MET) intensity level for each activity (kcal/min)[13,14] by duration (minutes), frequency (per 2 weeks), and months (per year) of exercise, divided by 24. For walking, different MET intensity scores were used depending on the reported usual pace. Data were missing at baseline regarding duration of exercise for 1.5%, frequency for 1.6%, and months per year for 3.0% of the participants. Missing data were imputed using single-regression imputation based on type of physical activity, duration of exercise, frequency per week, months per year, sex, age, race, and for walking, pace. Exercise intensity was based on MET intensity levels; activities with a MET intensity level below 4, such as walking, were considered low intensity; 4 to 6, such as gymnastics, moderate; and above 6, such as jogging, strenuous intensity.[6,14]

Statistical Analysis

Incidence rates (IRs), hazard ratios (HRs), and 95% confidence intervals (95% CIs) were calculated using survival analysis with exercise data from baseline and exercise modeled as a time-varying exposure, updated at each subsequent exercise assessment, using Cox regression analysis. The amount of exercise was categorized in three different ways: first as exercise versus no exercise (based on a cutoff of 500 kcal/wk); second, in four categories of exercise intensity (none, mild, moderate, and strenuous); and third, in six groups of kilocalories per week (0, 1–200, 201–500, 501–1,000, 1,001–1,500 and >1,500). All analyses were adjusted for sex, age, race, and body mass index (BMI; kg/m^2) at baseline and self-reported health status to provide adjusted hazard ratios (HR_{adj}). Models including baseline exercise were adjusted for baseline self-reported health, whereas models including exercise as a time-varying exposure were adjusted for self-reported health as time-varying covariate.

Separate analyses were performed for venous thrombosis events that were not related to cancer and for idiopathic venous thrombosis. One analysis was restricted to person-time and venous thrombosis events in the year after assessment of exercise. To assess the sensitivity of the results to competing risks such as death due to causes other than venous thrombosis, the cause-specific hazard model, in which participants who died from causes other than venous thrombosis were censored at the time of death, was compared with the crude incidence model, in which it was assumed that these participants would never have developed venous thrombosis by artificially extending the venous thrombosis-free survival time after death until the end of follow-up.

In addition, separate sensitivity analyses limited to healthy participants were performed. Participant was considered healthy if, at the current and all previous assessments, they reported good, very good, or excellent health status, no limitations in ADLs or IADLs, and no loss or gain of more than 10 pounds (4.5 kg) in any 1-year interval because of illness. Additionally, they were required to have no history of cancer or cardiovascular disease[2,15] at baseline.

Because BMI may be both a confounder and an intermediate variable in the association between exercise and venous thrombosis, all analyses were adjusted only for BMI at baseline. To further address this issue, a marginal structural model analysis was performed that allowed adjustment for the confounding effect but not for the intermediate effect of BMI.[16]

All analyses were performed in Stata/SE for Windows 8.0 (Statacorp, College Station, TX).

Results

Of the 5,888 participants in CHS, 5,534 had no history of venous thrombosis before baseline and were included in the present analysis. During a median of 11.6 years of follow-up, 171 participants developed a first venous thrombosis. At baseline, 2,081 participants (37.6%) expended≥500 kcal/wk or more on exercise (exercise group), and 3,453 participants (62.4%) expended less than 500 kcal (nonexercise group) per week. Participants who exercised were on average younger, more likely to be male and lean, less likely to be black, and had better self-reported health, more education, and higher income than participants who did not exercise .(Table 1).

Exercise at baseline was not associated with risk of venous thrombosis (Table 2). After adjustment for sex, age, race, self-reported health, and BMI at baseline, there was no association between exercise and the risk of venous thrombosis (HR_{adj}=1.16, 95% CI)=0.84–1.61). With exercise modeled as a time-varying exposure, findings were in the direction of higher risk of venous thrombosis associated with exercise (HR_{adj}=1.38, 95% CI=0.99–1.91, Table 2).

Table 2. Risk of Venous Thrombosis in All Subjects (n=5534) and in Healthy Participants (n=1807) in Relation to Sports Exercise at Baseline or with Exercise Modeled as a Time-Varying Exposure.

	Exercise*	Cases of venous thrombosis	Time at risk (person-y)	Incidence rate/1000 person-y	Hazard Ratio (CI§)	Hazard Ratio adjusted for sex, age, and race (CI§)	Hazard ratio adj (CI§)
All Participants							
Baseline	No	104	31675	3.28	1	1	1
	Yes	67	20633	3.25	0.98 (0.72 - 1.34)	1.03 (0.75 – 1.41)	1.16 (0.84 - 1.61)†
Time-varying exposure	No	110	34727	3.17	1	1	1
	Yes	61	17577	3.47	1.12 (0.83 - 1.55)	1.19 (0.86 – 1.64)	1.38 (0.99 - 1.91)‡
Healthy participants #							
Baseline	No	27	10169	2.66	1	1	1
	Yes	24	8605	2.79	1.04 (0.60 - 1.80)	1.10 (0.63 – 1.92)	1.16 (0.66 - 2.04)†
Time-varying exposure	No	11	7803	1.41	1	1	1
	Yes	14	5853	2.39	1.74 (0.79 - 3.83)	1.82 (0.82 – 4.05)	1.99 (0.89 - 4.48)‡

* Exercise: No is <500 kcal/week, Yes is ≥500 kcal/week
§ CI=95 percent confidence interval
† Adjusted for sex, age, race, body mass index at baseline and self-reported health at baseline
‡ Adjusted for sex, age, race, body mass index at baseline and self-reported health as time-varying covariate
# Restricted to no previous or current cancer, no history of cardiovascular disease at baseline, good, very good or excellent self-reported health, no impaired ADL or IADL at the most recent assessment, and no self-reported weight change of >10 lbs. due to illness in the year before the most recent exercise assessment

Further adjustment for income, education, ADLs, IADLs, smoking, and diabetes mellitus did not alter these findings. In an analysis limited to healthy participants (n=1,807), findings with exercise modeled as a time-varying exposure were again in the direction of greater risk (HR_{adj}=1.99, 95% CI=0.89–4.48, Table 2). All further analyses considered exercise as a time-varying exposure. Findings were in the direction of greater risk with exercise for venous thrombosis not related to cancer (n=133 events, HR_{adj}=1.38, 95% CI=0.95–2.00) and idiopathic venous thrombosis (n=65 events, HR_{adj}=1.69, 95% CI=1.00–2.83). Results were similar in groups defined according to age (<75 vs ≥75), BMI (<30 vs ≥30 kg/m^2), sex, race (black vs other races), and self-reported health status (excellent, very good or good vs fair or poor).

Table 3. Relation of Intensity of Exercise at Baseline or as a Time-Varying Exposure with Risk of Venous Thrombosis

Model	Intensity of exercise*	Cases of venous thrombosis	Time at risk (person-y)	Incidence rate /1000 person-y	Hazard ratio adj, with no exercise group as reference group (CI§)	Hazard ratio adj, with mild exercise intensity group as reference group (CI§)
Baseline	No exercise	58	13906	4.17	1 (ref)	
	Mild	37	14823	2.50	0.68 (0.45 - 1.04)†	1 (ref)
	Moderate	51	17393	2.93	0.81 (0.55 - 1.19)†	1.19 (0.78 - 1.83)†
	Strenuous	25	6185	4.04	1.28 (0.79 - 2.09)†	1.90 (1.13 - 3.19)†
Test for trend					p= .737	p= .024
Time-varying exposure	No exercise	63	16644	3.78	1 (ref)	
	Mild	32	13519	2.37	0.75 (0.49 - 1.16)‡	1 (ref)
	Moderate	50	16481	3.03	0.98 (0.67 - 1.43)‡	1.29 (0.83 - 2.02)‡
	Strenuous	26	5654	4.60	1.75 (1.08 - 2.83)‡	2.31 (1.36 - 3.94)‡
Test for trend					p= .121	p= .004

* No exercise= 0 kcal/week, Mild intensity exercise (METS<4) Moderate (METS 4-6), Strenuous (METS>6),

§ CI=95 percent confidence interval

†Adjusted for sex, age, race, body mass index, and self-reported health at baseline

‡Adjusted for sex, age, race, body mass index at baseline, and self-reported health as time-varying covariate

Mild-intensity exercise was associated with a slightly but not significantly lower adjusted risk of venous thrombosis than no exercise at all for exercise at baseline and for the time-varying analysis (Table 3).

In participants who exercised, strenuous-intensity exercise, such as jogging, was associated with greater risk of venous thrombosis than mild-intensity exercise, such as walking (test for trend in the fully adjusted time-varying analysis *P*=.004, Table 3). This trend remained after further adjustment for kilocalorie expenditure (test for trend *P*=.02). When five different categories of kilocalorie expenditure in exercise were studied, risk was slightly but not significantly lower for the two lowest kilocalorie exercise groups (1–200 and 201–500 kcal/wk) than for those who did not exercise at all (0 kcal/wk), whereas for those who exercised, the risk of venous thrombosis was greater with greater energy expenditure (test for trend in the fully adjusted time-varying analysis *P*=.02).

There were 43 venous thrombotic events that occurred within 1 year after an exercise assessment. Considering only person-time in the year after each exercise assessment, the HR_{adj} for exercise compared with no exercise was 1.46 (95% CI=0.75–2.84), with exercise modeled as a time-varying exposure. When testing the sensitivity of the results to competing risks, it was found that the HR_{adj} of 1.43 (95% CI=1.02–1.98) for the crude incidence model was similar to that of the cause-specific hazard model (HR_{adj}=1.38, 95% CI=0.99–1.91). The HR of the marginal structural model analysis again was in the direction of greater risk of venous thrombosis associated with exercise (HR_{adj}=1.51, 95% CI=1.00–2.26).

Discussion

In this observational study of elderly people, the findings were in the direction of greater venous thrombosis risk associated with exercise expending 500 kcal/wk or more than with less than 500 kcal/wk when exercise was modeled as time-varying exposure. Assessing the spectrum of exercise, participants who performed strenuous exercise or expended more kilocalories had a higher risk of venous thrombosis than those who performed mild-intensity exercise or expended fewer kilocalories.

Previous analysis of the LITE data with less follow-up time and thus fewer venous thrombotic events and an analysis in the Physicians' Health Study suggested that exercise was associated with greater risk of venous thrombosis.[6,7] No possible explanation for this greater risk was given. The current detailed analysis found a more-complex relationship, with a nonsignificantly lower risk of venous thrombosis associated with low-intensity exercise than with no exercise and a higher risk associated with high-intensity exercise. Two case-control studies reported a lower risk of venous thrombosis associated with exercise.[9,10] Participants included in these studies were on average younger than in the cohort studies.

In cohort studies, exercise habits were assessed before the venous thrombosis event, whereas in case-control studies, cases provided exercise information after the diagnosis. Although both case-control studies ascertained exercise habits for the period before the venous thrombotic event, it remains possible that the case subjects' knowledge of their diagnosis influenced the self-report of exercise.

The present study assessed exercise habits at only two or three time points; therefore, reported exercise might not be representative of the time period just before the venous thrombosis. To address this potential problem, the analysis was restricted to cases of venous thrombosis that occurred within 1 year after an exercise assessment, and similar results were found. Nonetheless, short-term changes in exercise habits just before the venous thrombosis were not captured in this study.

In the present study, exercise was self-reported, and the methods used to estimate exercise intensity and kilocalorie expenditure may not be accurate for each participant across the range of ages and fitness of study participants. Furthermore, only venous thrombosis cases that came to clinical attention were identified; it is possible that some cases were missed, but this is likely to be independent of exercise exposure.

When studying exercise, it is difficult to distinguish the relationship with exercise from effects of other factors that are related to exercise and venous thrombosis, such as general health. By adjusting for self-reported health status and BMI and by restricting the analysis to healthy participants, it was attempted to limit the confounding effects of health status on exercise, but residual confounding may have occurred.

Exercise at high levels may be associated with a higher rate of injuries in elderly people. Injuries are common; the National Center for Injury Prevention and Control estimated that in 2000, 7.5% of people aged 65 and older suffered from an unintentional nonfatal injury.[17] It is well known that greater exercise intensity, frequency, or duration leads to greater risk of injuries than lower levels of exercise.[18] Injuries can lead to decreased physical activity, immobility, and a hypercoagulable state.[19] As a consequence, major injuries are known to increase the risk of venous thrombosis,[20] and a recent analysis in the MEGA study indicated that even minor injuries such as sprains contribute to the occurrence of venous thrombosis.[21] Because the current study found a higher risk of venous thrombosis in subjects who performed strenuous-intensity exercise than in those who performed mild-intensity exercise, and elderly people are at greater risk of falling than younger people, an injury–venous thrombosis hypothesis seems plausible. Unfortunately, information regarding injuries not requiring hospitalization before the venous thrombotic event was not available, although analysis of the risk for idiopathic venous thrombosis, which excluded events following major trauma, produced results similar to those for all venous thrombosis events.

Several studies, including the CHS, have reported that, in elderly people, exercise is beneficial for longevity and is associated with a lower risk of cardiovascular disease.[22,23] Most studies have shown that moderate- and strenuous-intensity exercise are more beneficial than no exercise at all or mild-intensity exercise. The overall benefits of exercise likely outweigh the possible higher risk of venous thrombosis or injuries, but more research is needed to investigate this unexpected higher risk of venous thrombosis in elderly people associated with strenuous-intensity exercise.

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