Association of physical activity and recurrent venous thromboembolism

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Abstract

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Background
Preventing recurrent venous thromboembolism (VTE) will reduce further physical decline and fatalities among patients who have experienced an incident VTE. Understanding the role of moderate to vigorous physical activity (MVPA) in relation to VTE recurrence risk could help inform behavioral health recommendations.

Methods
The Heart and Vascular Health (HVH) study was set in a large integrated healthcare system with detailed medical and pharmaceutical records. The HVH study identified adults with an incident VTE between January 2002 and December 2010; an inception cohort was formed from these cases and adults were followed for a first recurrent VTE through December 2014. Information on usual MVPA pre-incident event was self-reported for 1381 adults via telephone interviews (TI) and MVPA was calculated in metabolic equivalent (MET) hours (h) per week.

Results
During follow-up (median=5.23 years), 288 (20.9%) individuals developed a recurrent VTE. Using adjusted Cox proportional hazards models, we found no evidence of an association between any MVPA compared to none in relation to VTE recurrence risk (HR_{adj}=1.24, [95% CI: 0.80, 1.91]). Our primary analyses of any MVPA in continuous MET h/week showed no evidence of an association between continuous MVPA and VTE recurrence risk (HR_{adj}=1.00, [95% CI: 0.98, 1.03]), nor evidence of an association of MVPA in quartiles (p-trend=0.62). Secondary analyses of MET-h/week of PA by intensity also showed no evidence of an association of moderate PA (HR_{adj}=1.00, [95% CI: 0.97, 1.03]) or vigorous PA (HR_{adj}=1.03, [95% CI: 0.99, 1.08]) with recurrent VTE risk.

Conclusions
In a cohort of adults with an incident VTE, energy expenditure in any MVPA and separately, within moderate and vigorous intensities of PA, was not associated with risk of recurrent VTE.

Introduction

In the United States, venous thromboembolism (VTE) is the third most common cardiovascular disease diagnosis, with a high risk of recurrence and adverse outcomes that cause physical decline and disability. Deep vein thrombosis (DVT) is the most frequent manifestation of VTE, which can result in post-thrombotic syndrome, a disabling complication of DVT, in 20-35% of patients.[1] VTE may also manifest as a pulmonary embolism (PE), with or without DVT. PE is associated with a high mortality rate and post-PE syndrome in nearly half of PE patients, which is increasingly understood to limit functionality.[1] VTE recurrence is frequent, with a recurrence rate of 7.8 per 100 person-years in the first year following a VTE,[2] and up to 30% of individuals experiencing a recurrent event within 10 years.[3] Established provoking factors for both incident and recurrent VTE include cancer, surgery, pregnancy, and estrogen therapies; however, recurrence risk is higher among unprovoked cases, and factors associated with unprovoked VTE are not well understood.[4]

Anticoagulant therapy is the standard of care to prevent a recurrent event in individuals who experience a first VTE, though it is associated with risks of bleeding.[5] Determination of the recommended duration of anticoagulant use at the patient-level depends on individual risk of recurrence, and anticoagulants do not eliminate recurrence. A variety of tools, such as the Vienna Prediction Model, have been developed to estimate individual recurrence risk after an unprovoked event.[6] These include established demographic and clinical factors such as sex, obesity, exogenous estrogen use, D-dimer levels, and location of first VTE.[7,8] Whether modifiable lifestyle behaviors, such as physical activity (PA), are associated with risk of VTE recurrence is largely unknown. Smoking[9] and dietary intake[10] may impact recurrence after an unprovoked event, and sleep apnea appears to be associated with risk of PE recurrence.[11] Sedentary behavior, independent of PA, has been tied to a greater risk of VTE recurrence.[5,12,13]

Research about PA and incident VTE risk has provided inconclusive results, with some studies indicating a lower risk of VTE with greater amounts of PA, and others indicating a U-shaped association, with high levels of PA tied to higher risk of VTE.[5] To our knowledge, the role of PA in relation to VTE recurrence risk has been explored in only one study, with null results; however, this study did not evaluate whether continuous amounts of PA or characteristics of PA such as within intensity level were associated with recurrence risk.[14] The authors compared groups based on time spent in “light” and “hard” PA and do not include a moderate group or specify whether they evaluated these groups independently or if there is crossover; corresponding results were not reported.

Our study primarily aimed to evaluate the association of total energy expended per week in any moderate-to-vigorous physical activity (MVPA) prior to the incident VTE event with recurrent VTE risk among adults in the Heart and Vascular Health (HVH) study. Secondarily, we aimed to evaluate energy expended per week in PA by intensity level with recurrent VTE risk. We hypothesized that risk of recurrence would be lower among individuals with greater energy expenditure in MVPA prior to their incident event. We also hypothesized that more moderate intensity PA in particular would be associated with lower risk of recurrence, while more vigorous PA may be associated with greater risk of recurrence. Participants retrospectively self-reported MVPA before their incident VTE, which we considered to be a measure representative of habitual MVPA. By evaluating MVPA continuously and within quartiles among those who participated in any MVPA, we aimed to evaluate both continuous associations and whether a dose-response relation may exist.

We also aimed to evaluate interaction between MET-h/week in any MVPA and the following factors, separately, in relation to recurrent VTE risk: provoked vs. unprovoked classification of the incident event, incident event location (proximal DVT alone, distal DVT alone, PE with or without DVT), time from incident VTE to telephone interview, and obesity status.

Methods

Study Setting & Design

This population-based study was set within Group Health Cooperative (GHC), an integrated healthcare system in Western Washington State, now Kaiser Permanente Washington.[16] The HVH case-control study identified incident VTE cases among GHC members between 2002 and 2010.[7] An inception cohort was formed from these individuals and they were followed for recurrent VTE events. HVH study protocols were approved by the institutional review board at GHC and the University of Washington.

Study Participants

Study participants were men aged 30-89 years and women aged 18-89 years who experienced an incident VTE event from January 2002 through December 2010. All participants were GHC members at the time of their incident event. International classification of diseases, version 9 (ICD-9) diagnostic codes as well as anticoagulant prescriptions were used to identify possible incident VTE events, including DVT or PE, from inpatient and emergency visits.[16] Trained abstractors reviewed GHC medical records for each potential VTE event to verify diagnoses. Validated incident VTE events were those with positive diagnostic imaging test results (98% of eligible cases), fatal PE, or physician-diagnosed cases.[16]

Incident thrombus location was classified using imaging and physician diagnoses: proximal DVT, distal DVT, or PE with or without DVT.[7] Incident events were further categorized as provoked or unprovoked. Provoking risk factors included the following: cancer diagnosis or treatment within 2 years prior to the incident event; major hospitalization within 3 months, or minor hospitalization within 2 months; surgery within 2 months prior to the incident event; major fracture within 2 months prior to the incident event; pregnancy or puerperium at or within 2 months prior to the incident event; current use of estrogen hormone therapy (HT) at 80% prescription compliance or oral contraceptives (OC) use in the past 2 months.[16–18]

Inclusion in this study further required completion of a telephone interview (TI) post-incident VTE, during which PA exposure information was collected on PA prior to their index event. Among HVH participants, 2844 incident VTE cases were identified and followed for recurrence; of these, 896 died prior to the TI and 237 individuals were not invited to complete the TI due to administrative reasons. We invited 1711 living individuals to complete the TI and 1381 (81%) completed the full-length TI and had non-missing data on PA. Non-missing PA data was defined as non-missing responses for all 23 activities asked about in all TI versions. Missing values for PA frequency and/or duration were imputed using the median value among incident VTE cases.

Data Collection

Recurrent VTE Events

A recurrent VTE was defined as the detection of a thrombus in a new location any time after the incident event or an extended thrombus occurring in the same location at least 14 days after the incident event.[7,16] Possible recurrent VTE events were identified by ICD-9 codes; these events

were reviewed and validated by trained medical record abstractors who were unaware of study hypotheses. Qualifying events required clinical evidence such as imaging or anticoagulant initiation. Thrombus location and provoking factors were recorded for each recurrent event. Follow-up for recurrences ended in December 2014.

Physical Activity

Usual, self-reported PA during the month before the incident VTE was ascertained retrospectively through TI. The TI asked about participation in 23 specific types of PA during the month prior to the incident event, using an instrument originally derived from the Minnesota Leisure-Time Activity questionnaire.[19] Individuals could also self-report participation in other types of activities. Information on frequency and duration of each activity was obtained by asking about: (1) the number of times each activity was done per month ("during [month prior to reference date], how many times a month did you [fill activity]?"); and (2) the average amount of time per session ("what was the average amount of time you spent [fill activity] each time? [hours and minutes])."

Any MVPA over the month prior to the incident event was estimated in metabolic equivalent hours per week (MET-h/week), using activity-specific metabolic equivalent (MET) intensity levels (supplementary **Table S1**).[20] To calculate MET-h/week for each activity, we multiplied the MET value by frequency (times per month) and duration (hours), and divided by 4.35 (weeks per month).[21] Activities were categorized by intensity as moderate (MET intensities 3-<6) or vigorous (MET intensities ≥6); the TI did not ask about activities of light intensity (MET intensities <3).[22,23] Given these categorizations, walking (MET=4) for exercise was included with moderate intensity.[21] Total MET-h/week while participating in any MVPA was calculated as the sum of MET-h/week across all activities for each individual. MET-h/week in moderate PA was calculated by summing total MET-h/week in moderate PA for each person; the same was done for vigorous PA.

Covariates

Trained medical abstractors reviewed GHC records from before the incident VTE through the end of follow-up or death to collect clinical data and information about comorbid conditions. Behavioral information at the time of the incident VTE was collected via the TI, and other covariate information was collected from the GHC medical record, including sex, age, height and weight, smoking, and pregnancy. Individuals with BMI ≥30 were classified as obese, and those with BMI <30 as not obese.[24] Population group was self-reported for those participating in the TI. Dates of cancer diagnoses and treatments were collected from chart review and electronic health record data; hospitalizations, inpatient surgeries, and major fractures were collected from chart review and GHC administrative records. Anticoagulation start and stop dates were collected from chart review and prescription fill records. Oral estrogen hormone therapy and contraceptive use was determined from prescription fills.[16]

Statistical Analyses

We described demographic and health-related characteristics using medians and interquartile ranges (IQRs) or percentages among adults with no MVPA and across quartiles of energy expended. To estimate the association between total energy expended per week in MVPA and risk of VTE recurrence, we used Cox proportional hazards regression models. Individual time at risk began on day 15 after the incident VTE and continued until the first recurrence, or until individuals were censored due to death or end of follow-up.

An initial analysis evaluated the risk of recurrent VTE associated with any MVPA compared with none. Primary analyses evaluated a continuous measure of MVPA in MET-h/week to evaluate a potential linear relationship between total energy expended in MVPA and recurrent VTE risk. In separate analyses we categorized MVPA into quartiles to evaluate a potential dose-response association between total energy expended in MVPA and recurrent VTE risk. Secondary analyses within MVPA intensity level separately modeled total energy expended in moderate and vigorous intensity PA, continuously and in quartiles. Point estimates associated with continuous measures of PA were estimated for each 7.5 MET-h/week difference to improve interpretability, representing about 21 or less minutes per day of moderate PA or 15 or less minutes per day of vigorous PA (values represent estimates for the lowest MET intensity scores within each intensity category).[15] The Physical Activity Guidelines for Americans recommends 150 minutes of moderate activity or 75 minutes of vigorous intensity activity per week,[15] which equals an average of ~21 minutes per day of moderate intensity PA or ~11 minutes per day of vigorous intensity PA.

We estimated hazard ratios (HR) and 95% confidence intervals (CI) for the association between energy expended per week in MVPA and risk of VTE recurrence using a series of models adjusted for confounders identified *a priori.* Likely confounders that influence participation in MVPA and underlying risk of recurrent VTE include demographic factors such as sex and age, smoking status, a range of provoking factors and BMI.[7,8] Use of anticoagulants may influence risk of recurrence over time and was included as a precision variable.[5] In an initial model we adjusted for demographic factors: age (continuous), sex, and population group. A second model further adjusted for smoking (never, past, current) and incident event provoking factors, separately (cancer, hospitalization, fracture, surgery, pregnancy, and HT or OC use). A third model further adjusted for BMI (continuous); the final model also adjusted for time-varying anticoagulant use. Participants with missing values for BMI (n=1), time-to-TI (n=1), and location (n=23) were removed from the analysis. We assessed deviations from the proportional hazards assumption using Schoenfeld residuals.

To test for evidence of interaction between MET-h/week in MVPA and incident event location (proximal DVT, distal DVT, PE with or without DVT), incident event provoking status (provoked vs. unprovoked), time-to-TI, and obesity status, separately, we used the likelihood ratio test. In secondary analyses, we stratified analyses by factors with significant evidence of interaction (likelihood ratio $p<0.05$). To identify potential response bias, we described demographics of individuals with an incident VTE who did and did not complete the TI. A sensitivity analysis was performed to evaluate risk after stopping anticoagulation by restricting time at risk to begin after anticoagulant use ended. To account for outliers in continuous analyses, in sensitivity analyses we winsorized the MVPA, moderate PA, and vigorous PA MET-h/week values and ran continuous analyses using these winsorized values; all values above the 99th percentile were set to the 99th percentile. All analyses were run in R, version 4.3.2.[18]

Results

Participant characteristics for the 1381 adults with an incident VTE who completed the TI are presented in **Table 1**. At the time of the incident VTE, the population had a median age of 62 years, a BMI of 30.1 kg/m^2, was 59% female, and was 90% White. Anticoagulant use at the time of the incident VTE or within 30 days was 98.9%. Incident VTEs were 35.5% proximal DVTs, 10.4% distal DVTs, and 52% PEs with or without DVT. The median time from the incident VTE to the TI was about 2 years. Comparisons between those who did and did not complete the TI can be found in the supplement (supplementary **Table S2**). Individuals who did not complete the TI were on average older, were more likely to have smoked, and had a greater prevalence of cancer and hospitalization at baseline. Of the 1457 individuals who did not complete the TI, 896 (61%) were no longer alive at the time of the TI.

Individuals who reported no MVPA were more likely to have cancer (16.9%), recent hospitalization (30.3%), or fracture (9.2%), and more likely to smoke currently or in the past (59.9%) than individuals with MVPA (**Table 1**). Among adults with any MVPA, median BMI was higher among adults in lower quartiles of MVPA.

During the month before their incident event, 89% of individuals reported participating in any MVPA; of these, 88% did some moderate PA, and 48% did some vigorous PA. The most common activities were housework (71%) and walking (53%); other common activities were gardening (28%), exercise cycling (14%), and swimming (12%) (**Table S1**). The median energy expended in any MVPA was 22.9 MET-h/week, the mean was 35.5 MET-h/week, and the maximum was 295.4 MET-h/week. We reviewed activities for adults with >200 MET-h/week to identify potential errors, but the activity patterns seemed to be plausible. Upon excluding household and/or occupational activities (housework, gardening, mowing, and raking) the median energy expenditure in any MVPA was 16.1 MET-h/week, the mean was 27.0 MET-h/week, and the maximum was 289.7 MET-h/week.

Participants were followed for a median of 5.23 years (IQR: 2.99), and a maximum of 10.17 years. Among 1381 eligible participants, there were a total of 288 recurrent events, and the median time to recurrence was 2.85 years (IQR: 3.18). Survival curves for participation in any MVPA vs none as well as by quartiles of MVPA are presented in **Figure 1**. In a final adjusted model, there was no evidence of an association between any MVPA (>0 MET-h/week) and the risk of VTE recurrence, compared to those with no MVPA (0 MET-h/week) (HR_{adj}=1.24 [95% CI: 0.80, 1.91]) (**Table 2**).

Among individuals with any MVPA, there was no evidence of an association between continuous MET hours/week of MVPA and VTE recurrence risk (HR_{adj} per 7.5 MET-h/week=1.00 [95% CI: 0.98, 1.03]) (**Table 2**). There was also no evidence of an association between higher quartiles of MVPA and recurrence risk, compared to the lowest quartile of MVPA (p-trend=0.62).

Among participants with any moderate intensity PA, there was no evidence of an association between energy expenditure in moderate intensity PA and VTE recurrence risk (HR_{adj} per 7.5 MET-h/week=1.00 [95% CI: 0.97, 1.03]), and there was no evidence of a trend among quartiles of moderate PA (p-trend = 0.63) (**Table 3**). Similarly, among participants with any vigorous intensity PA, there was no evidence of an association between energy expenditure in vigorous intensity PA and recurrence risk (HR_{adj} per 7.5 MET-h/week=1.03 [95% CI: 0.98, 1.08]), and there was no evidence of a trend among quartiles of vigorous PA (p-trend=0.78).

We found significant interaction of obesity with both continuous vigorous PA (likelihood ratio p=0.008) and quartiles of vigorous PA (likelihood ratio p=0.005); no evidence was found for interaction of obesity with any MVPA or moderate intensity PA. Among adults without obesity (n=355), each additional 7.5 MET hours/week of vigorous PA was associated with a 6% greater hazard of recurrence (HR_{adj}=1.06, [95% CI: 1.02, 1.11]), but there was no evidence of an association between continuous vigorous PA and recurrence risk among adults with obesity (**Table 4**). Among adults with obesity, there was evidence of a trend across quartiles of vigorous PA, but no evidence of significant association within any quartile (p-trend=0.0003) (**Table 4**); there was no evidence of a trend across quartiles of vigorous activity among adults without obesity.

No significant interaction of MVPA (any MVPA or by intensities of PA) with incident event location, incident event provoking factors, or time-to-TI was found. Results from sensitivity analyses that began time at risk at first cessation of anticoagulation were similar to those from primary analyses. Results from analyses using MVPA exposures that had been winsorized at the 99th percentile were not meaningfully different from primary results. (supplementary **Table S3**). We found no evidence of non-proportional hazards (all p>0.05).

Table 1. Baseline characteristics of eligible Heart and Vascular Health study participants who experienced an incident venous thromboembolism, overall, among adults with no moderate-to-vigorous physical activity (MVPA), and by quartiles of MET hours per week from any MVPA.

			Any MVPA: Quartiles of MET-h/week			
Characteristic	**Overall** (n=1381)	**No MVPA** (n=142)	**Q1** [0.1-9.5 MET-h/week] (n=310)	**Q2** [9.6-22.8 MET-h/week] (n=309)	**Q3** [22.9-46.6 MET-h/week] (n=310)	**Q4** [46.7-295.0 MET-h/week] (n=310)
Median age, years (IQR)	62.0 (20.2)	64.5 (19.7)	61.9 (18.7)	60.3 (21.0)	60.2 (20.6)	63.3 (19.6)
Female, n (%)	820 (59.4)	90 (63.4)	208 (67.1)	197 (63.8)	167 (53.9)	158 (51.0)
Median BMI*, kg/m^2 (IQR)	30.1 (8.8)	31.2 (8.9)	32.5 (10.1)	30.4 (9.1)	29.2 (7.7)	28.2 (7.3)
Population Group						
Asian, n (%)	16 (1.2)	1 (0.7)	4 (1.3)	1 (0.3)	6 (1.9)	4 (1.3)
Black, n (%)	68 (4.9)	8 (5.6)	17 (5.5)	16 (5.2)	15 (4.8)	12 (3.9)
Native American/Alaska Native, n (%)	21 (1.5)	0 (0.0)	2 (0.6)	8 (2.6)	3 (1.0)	8 (2.6)
Pacific Islander, n (%)	5 (0.4)	1 (0.7)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
White, n (%)	1248 (90.4)	129 (90.8)	281 (90.6)	277 (89.6)	277 (89.4)	284 (91.6)
Other, n (%)	23 (1.7)	3 (2.1)	5 (1.6)	6 (1.9)	8 (2.6)	1 (0.3)
Smoking						
Never, n (%)	715 (51.8)	57 (40.1)	166 (53.5)	168 (54.4)	163 (52.6)	161 (51.9)
Past, n (%)	540 (39.1)	66 (46.5)	120 (38.7)	107 (34.6)	125 (40.3)	122 (39.4)
Current, n (%)	126 (9.1)	19 (13.4)	24 (7.7)	34 (11.0)	22 (7.1)	27 (8.7)
Incident event provoking factors[1]						
Cancer, n (%)	141 (10.2)	24 (16.9)	31 (10.0)	35 (11.3)	29 (9.4)	22 (7.1)
Hospitalization, n (%)	298 (21.6)	43 (30.3)	78 (17.3)	58 (18.8)	61 (19.7)	58 (18.7)
Surgery, n (%)	251 (18.2)	28 (19.7)	65 (21.0)	55 (17.8)	55 (17.7)	48 (15.5)
Fracture, n (%)	52 (3.8)	13 (9.2)	10 (3.2)	13 (4.2)	9 (2.9)	7 (2.3)

Pregnancy[2], n (%)	11 (1.3)	0 (0.0)	1 (0.5)	7 (3.6)	2 (1.2)	1 (0.6)
HT/OC use[2], n (%)	195 (23.8)	15 (16.7)	46 (22.1)	41(20.8)	55 (32.9)	38 (22.1)
Anticoagulant use[3], n (%)	1366 (98.9)	140 (98.6)	309 (99.7)	304 (98.4)	305 (98.4)	308 (99.4)
Incident VTE event location						
Proximal DVT, n (%)	487 (35.3)	57 (40.1)	97 (31.8)	102 (33.8)	126 (41.9)	105 (34.7)
Distal DVT, n (%)	144 (10.4)	12 (8.5)	33 (10.8)	34 (11.3)	34 (11.3)	31 (10.2)
PE with or without DVT, n (%)	718 (52.0)	69 (48.6)	175 (57.4)	166 (55.0)	141 (46.8)	167 (55.1)
Unknown	32 (2.3)	4 (2.8)	5 (1.6)	7 (2.3)	9 (2.9)	7 (2.3)
Median time to TI, years (IQR)	2.03 (1.9)	1.9 (1.7)	2.0 (1.3)	2.0 (1.7)	2.2 (2.6)	2.1 (2.2)

Q = quartile; MET-h/week = metabolic equivalent hours per week; PA = physical activity; MVPA = Moderate to vigorous physical activity; IQR = interquartile range; BMI = body mass index; kg = kilograms; HT = hormone therapy; OC = oral contraceptive; VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism; TI = telephone interview.

* Missing 1 value; calculated for n=1386

[1] Defined as cancer diagnosis or treatment within the 2 years prior to incident VTE; hospitalization for at least 3 days within the 3 months prior to incident VTE, or less than 3 days within the 2 months prior to incident VTE; inpatient surgery in the 2 months prior to incident VTE; major fracture within 2 months prior to incident VTE; pregnancy or puerperium at or within 2 months prior to incident VTE; prevalent HT/OC use at the time of incident event.

[2] Among female participants (n=826)

[3] Defined as prevalent use at the time of the incident VTE, or use starting within 30 days

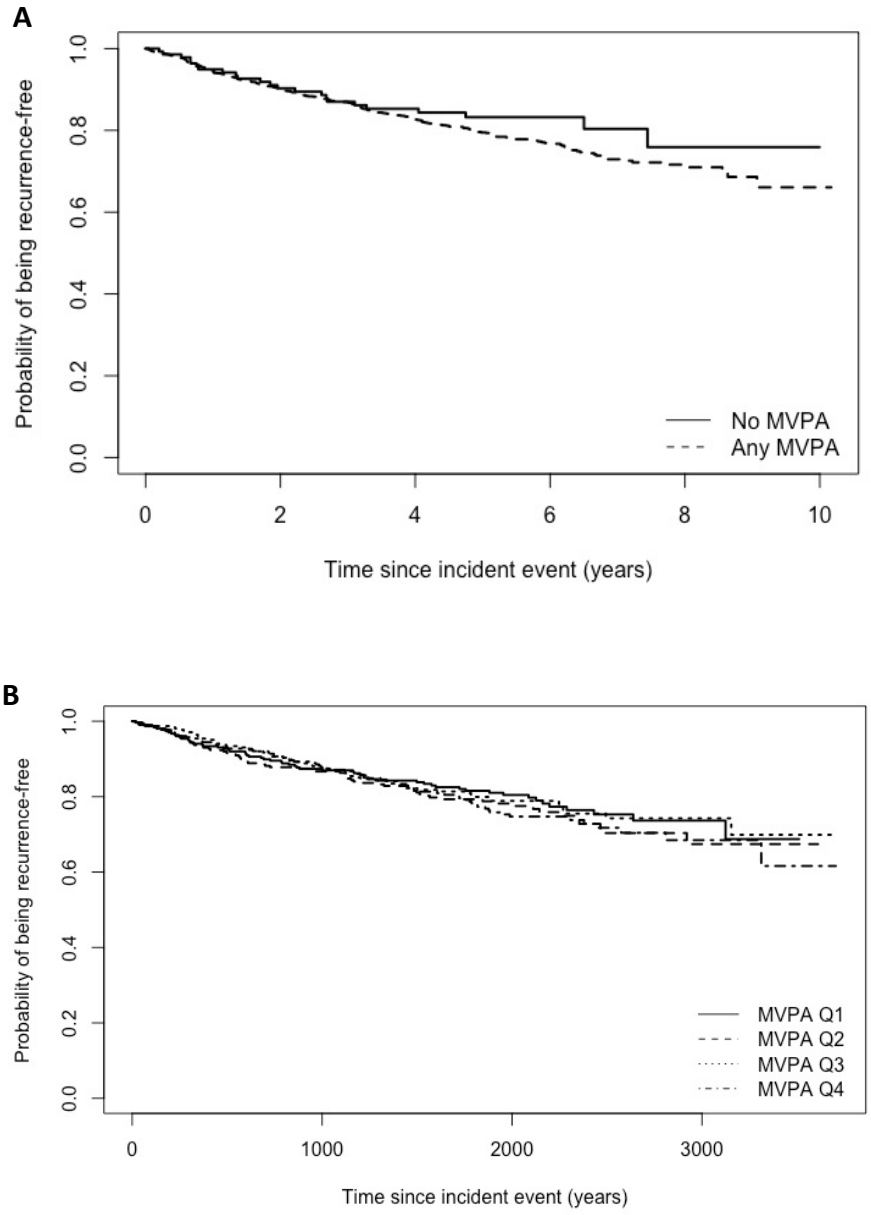

Figure 1. Kaplan Meier survival curves for VTE recurrence over time for (A) participation in any MVPA compared to no MVPA, and (B) quartiles of any MVPA.

Table 2. Association of energy expenditure in moderate-to-vigorous physical activity with recurrent venous thromboembolism

	n	Events	Person-years of follow-up	First adjusted HR* (95% CI)	Final adjusted HR* (95% CI)	*P*-value
Analyses including individuals with no MVPA						
Any MVPA vs None						
No MVPA (0 MET-h/week)	142	23	653.7	1.00 [ref]	1.00 [ref]	-
Any MVPA (>0 MET-h/week)	1239	265	5839.7	1.31 (0.86, 2.01)	1.24 (0.80, 1.91)	0.33
Analyses only among individuals with any MVPA						
Continuous MVPA, per 7.5 MET-h/week**	1239	265	5839.7	1.00 (0.98, 1.02)	1.00 (0.98, 1.03)	0.72
Quartiles among those with MVPA						
Q1 (0.1-9.5 MET-h/week)	310	61	1452.6	1.00 [ref]	1.00 [ref]	-
Q2 (9.6-22.8 MET-h/week)	309	68	1398.8	1.17 (0.83, 1.65)	1.21 (0.84, 1.72)	0.31
Q3 (22.9-46.6 MET-h/week)	310	63	1482.9	0.98 (0.68, 1.39)	1.00 (0.70, 1.44)	0.99
Q4 (46.7-295.0 MET-h/week)	310	73	1505.5	1.10 (0.78, 1.56)	1.17 (0.82, 1.68)	0.39
P for trend: 0.62						

HR = hazard ratio; CI = confidence interval; MVPA = moderate to vigorous physical activity; MET-h/week = metabolic equivalent hours per week; Q = quartile; ref = reference; n = sample size.
* Four total adjustment models: the first model adjusted for only age, sex, and population group. The final model also adjusted for BMI, smoking, incident event provoking factors (cancer, hospitalization, major surgery, major fracture, pregnancy, and HT or OC use), and time-varying anticoagulation use.
** ~150 min/week moderate intensity PA

Table 3. Association of energy expenditure within physical activity intensity levels with recurrent venous thromboembolism risk, among participants who did any moderate to vigorous physical activity

	n	Events	Person-years of follow-up	First adjusted HR* (95% CI)	Final adjusted HR* (95% CI)	*P*-value
Moderate PA (MET 3-<6)						
Continuous, per 7.5 MET-h/week**	1209	258	5710.2	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)	0.92
Quartiles among those with moderate PA						
Q1 (0.01-7.23 MET-h/week)	295	65	1366.1	1.00 [ref]	1.00 [ref]	-
Q2 (7.24-16.12 MET-h/week)	309	56	1453.2	0.81 (0.57, 1.16)	0.85 (0.58, 1.24)	0.39
Q3 (16.13-32.78 MET-h/week)	302	64	1410.9	0.93 (0.66, 1.31)	0.95 (0.66, 1.36)	0.79
Q4 (32.79-269.8 MET-h/week)	303	73	1479.9	1.00 (0.72, 1.41)	1.08 (0.75, 1.53)	0.69
P for trend: 0.63						
Vigorous PA (MET ≥6)						
Continuous, per 7.5 MET-h/week**	664	144	3133.0	1.02 (0.97, 1.06)	1.03 (0.98, 1.08)	0.20
Quartiles among those with vigorous PA						
Q1 (0.01-3.44 MET-h/week)	157	19	441.8	1.00 [ref]	1.00 [ref]	-
Q2 (3.45-10.97 MET-h/week)	175	24	554.5	1.23 (0.77, 1.97)	1.27 (0.78, 2.09)	0.34
Q3 (10.98-25.32 MET-h/week)	166	29	482.7	0.97 (0.59, 1.59)	1.05 (0.63 1.77)	0.84
Q4 (25.33-229.9 MET-h/week)	166	27	488.4	1.04 (0.63, 1.70)	1.14 (0.67, 1.92)	0.63
P for trend: 0.78						

HR = hazard ratio; CI = confidence interval; PA = physical activity; Q = quartile; MET = metabolic equivalent; MET-h/week = metabolic equivalent hours per week; ref = reference.
* Four total adjustment models: the first model adjusted for only age, sex, and population group. The final model also adjusted for BMI, smoking, incident event provoking factors (cancer, hospitalization, major surgery, major fracture, pregnancy, and HT or OC use), and time-varying anticoagulation use.
** ~150 min/week moderate intensity PA

Table 4. Association of energy expenditure in vigorous physical activity with recurrent venous thromboembolism (VTE), stratified by obesity status

Obesity status at time of incident VTE	**Adults without Obesity**			**Adults with Obesity** (n=309)		
	n	**Adjusted HR* (95% CI)**	***P*-value**	**n**	**Adjusted HR* (95% CI)**	***P*-value**
Continuous Vigorous PA, per 7.5 MET-h/week**	355	1.06 (1.02, 1.11)	0.008***	309	1.17 (0.68, 2.02)	0.58
Overall *P* for interaction: 0.0098						
Quartiles among those with vigorous PA						
Q1 (0.01-3.44 MET-h/week)	69	1.00 [ref]	-	88	1.00 [ref]	-
Q2 (3.45-10.97 MET-h/week)	82	0.92 (0.41, 2.07)	0.85	93	1.42 (0.61, 3.29)	0.41
Q3 (10.98-25.32 MET-h/week)	96	0.94 (0.44, 2.01)	0.87	70	1.08 (0.44, 2.58)	0.87
Q4 (25.33-229.9 MET-h/week)	108	1.61 (0.76, 3.39)	0.22	58	0.41 (0.14, 1.23)	0.11
P for trend			0.22			0.0003***
Overall *P* for interaction: 0.014						

HR = hazard ratio; CI = confidence interval; MVPA = moderate to vigorous physical activity; Q = quartile; MET-h/week = metabolic equivalent hours per week; ref = reference.

* Four total adjustment models: the first model adjusted for only age, sex, and population group. The final model also adjusted for BMI, smoking, incident event provoking factors (cancer, hospitalization, major surgery, major fracture, pregnancy, and HT or OC use), and time-varying anticoagulation use.

** ~75 min/week vigorous intensity PA

*** Significant at p<0.05

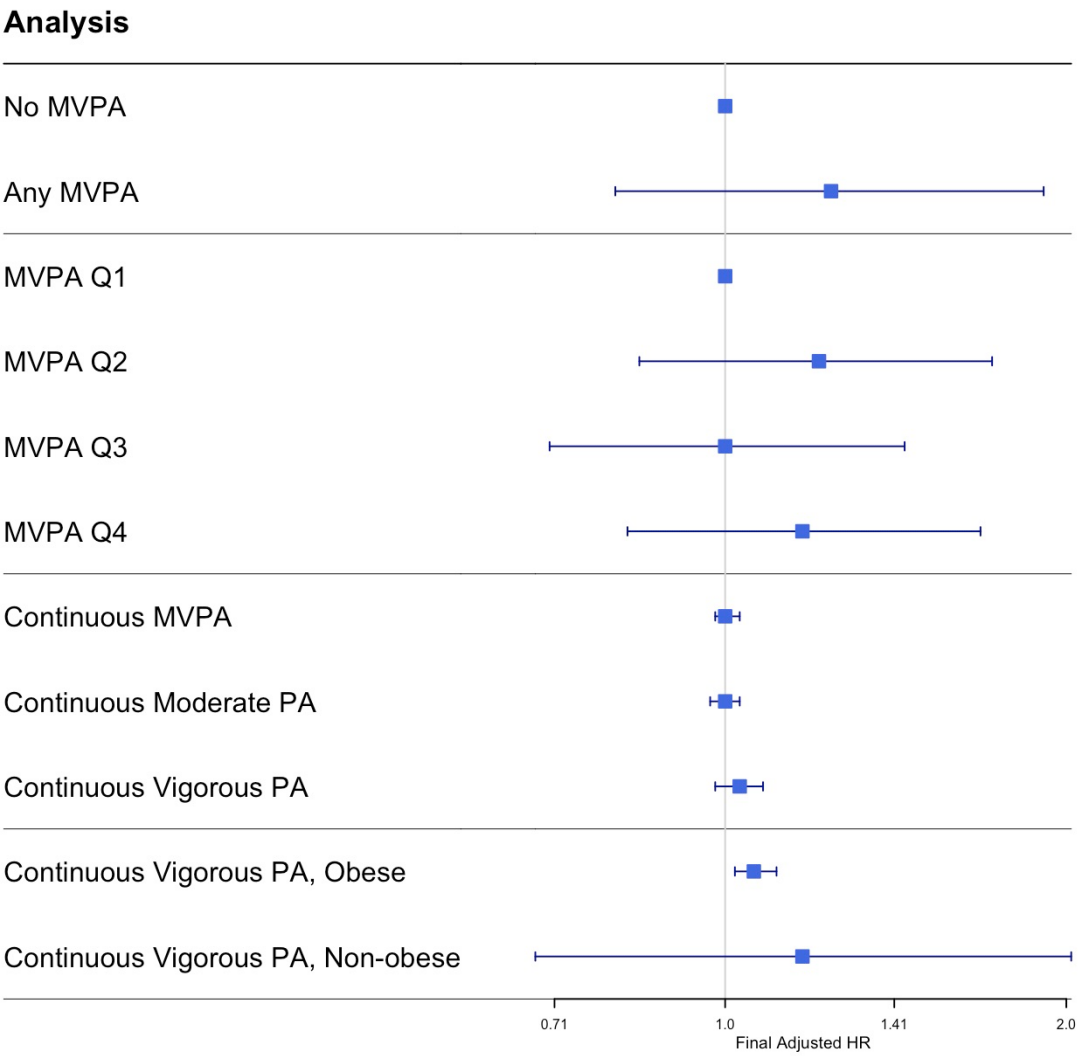

Figure 2. Forest plot of hazard ratios for analyses of PA and recurrent VTE

Discussion

We evaluated the association between MVPA and recurrent VTE risk over time, using data from an inception cohort of adults with an incident VTE in the HVH study. We hypothesized that greater energy expenditure in MVPA (MET-h/week) would be associated with a lower risk of recurrent VTE; however, we found no evidence of a significant association either linearly or by dose. Similarly, in evaluations of energy expenditure within intensity level, we found no evidence of significant associations with moderate or vigorous intensity PA. Energy expenditure in moderate PA and vigorous PA alone appeared to have no impact on recurrence.

These results align with a similar study on MVPA and VTE recurrence which found no evidence of significant associations between MVPA and recurrence risk.[14] Our study has nearly twice the sample size (n=1381 vs n=786) and has a much shorter time lag from the index event time to the time of the MVPA questionnaire (a mean of 2 years vs 5.5 years). This previous study found no evidence of an association for active individuals compared to inactive (HR=1.53, [95% CI: 0.77-3.05]), which is similar to our results for any MVPA compared to none (HR_{adj}=1.24 [95% CI: 0.80, 1.91]). Light intensity PA (MET score <3) was not collected in either study, and therefore the "inactive" or "no MVPA" groups likely include light PA. They did not present their results within intensities of PA. Some prior studies of MVPA and incident VTE risk found a higher risk of incident VTE with greater MVPA among adults.[5,21] In contrast, research into incident VTE and moderate PA alone has indicated a beneficial association, though inconsistent across some studies; in our study we did not see lower risk of recurrent VTE with moderate PA.[5,25] There is evidence of higher risk of incident VTE with more strenuous PA, which aligns with our results for non-obese individuals participating in vigorous PA.[5,25]

Obesity status appears to modify the association between vigorous PA and recurrent VTE risk. Among individuals without obesity, the risk of recurrent VTE was 6% greater for each additional 7.5 MET-h/week of vigorous PA. Expending 7.5 MET-h/week corresponds to about 15 minutes or less of vigorous PA each day on average; more vigorous activities with higher MET intensity scores would correspond to even shorter durations of vigorous PA. However, our study is not powered to detect an association of this size, so further research is needed. For individuals with obesity, there was evidence of a trend of decreasing VTE recurrence risk with increasing vigorous PA. Obesity is known to be a substantial risk factor for incident VTE, and though results are mixed for recurrence, obesity is included as a risk factor in prediction models for recurrent VTE.[6,8,26] A study on obesity and incident VTE found that MVPA modified the effect, resulting in greater risk for obese individuals who were active relative to inactive; this may indicate a lower baseline risk among active individuals.[27] Our results indicate reduced risk of recurrence with greater amounts of vigorous PA among obese individuals.

Participants in our study self-reported high total amounts of MVPA. Per the 2018 Physical Activity Guidelines for Americans, the minimum recommended MVPA is 150 minutes of moderate PA per week, or 7.5 MET-h/week; the higher recommended MVPA range for additional health benefits is at least twice that amount: ≥300 minutes of moderate PA per week, or 15 MET-h/week.[28] The median energy expenditure in our population was 22.9 MET-h/week, which is about 1.5 times the higher MVPA recommendation for additional health benefits; the 75th percentile was 46.6 MET-h/week, which is about 3 times the higher MVPA recommendation. Data from the 2018 National Health Interview Survey indicated 37.4% of individuals met the higher guideline.[28] It is evident that our HVH population reported higher levels of MVPA than the general US population, with 50% reporting about 1.5 times the upper end of the MVPA recommendation. However, our participants' self-report of PA included both leisure time PA and household and/or occupational activities, whereas the National Health Interview Survey asked participants only about leisure time PA; thus, we would anticipate that HVH participants' reported energy expenditure would be higher because it is inclusive of a longer activity list. We examined high energy expenditure totals over 200 MET-h/week, which

appeared to be feasible, although uncommon, behavior patterns. In sensitivity analyses reducing the highest PA values to the 99th percentile, results were not meaningfully different. Because participants were asked about each type of activity separately, it is possible that individuals over-reported their frequency or duration of participation in individual activities, resulting in an overestimated total MVPA when summed. Frequency and intensity are often overreported for activities participated in sporadically;[29] further, self-reported MVPA has been found to be higher than when measured directly with accelerometers.[30]

A high number of hours of moderate PA, especially walking and housework, contributed to the greatest values in our cohort. While the HVH questionnaire aimed to capture leisure-time MVPA, it did include questions about activities that may be household or occupational in nature: housework, gardening, mowing, and raking. When these household/occupational activities were removed, we found lower, though still high, MVPA (median=16.1 MET-h/week; maximum=289.7 MET-h/week). Because these activities tend to be more sporadic, there is a greater chance that they are overreported. [29] Consideration of socioeconomic risk factors may also influence decisions to include or exclude occupational activities. Individuals of lower socioeconomic status are less likely to participate in leisure-time MVPA, but more likely to report occupational MVPA.[31] While our study did not specifically evaluate leisure-time MVPA, it captured self-reported MVPA across a variety of activities relevant to adults across a range of socioeconomic status; however, we did not have adequate data to adjust for socioeconomic status in our models.

Public Health Relevance

Understanding whether MVPA pre-incident event is associated with VTE recurrence may help clinicians and patients make informed decisions about lifestyle behaviors. The TI in the HVH study asked about PA during the month prior to the incident event; however, the TI was administered on average 2 years after an incident VTE. If these reported PA habits remained similar in the time following the incident event, these results could be applicable to post-incident event PA. One study found that a majority of patients are able to resume usual levels of PA by four months after a VTE.[32] Our findings do not indicate that moderate PA during the month prior to an incident VTE may reduce, or increase, risk of recurrence. Given that obesity may be a risk factor for recurrence,[26] participation in moderate PA may be advisable especially for reducing BMI; whether a high amount of vigorous PA reduces risk among obese adults requires additional research. For non-obese adults, there may be a slightly greater risk of recurrence with vigorous PA; increased risk of incident VTE has been tied to strenuous PA, and further research regarding this association is needed to inform clinical guidance.[5,25] While vigorous PA may potentially increase risk of recurrence in the general population, further studies must be done to confirm this.

Strengths and Limitations

Strengths of our study include evaluations of both total energy expenditure in MVPA as well as energy expenditure within intensity levels. Classification of each activity as moderate or vigorous built on previous HVH research using the 2024 Compendium of Physical Activity MET scores, which is a standard, comparable system.[22] The HVH study population is likely representative of a broad group within the Pacific Northwest region of the United States. We have complete, reliable data on incident and recurrent events, which were identified using ICD codes and adjudicated. Accurate identification of incident VTE events is evidenced by nearly 99% of our cohort being on anticoagulants within 30 days of the index date. Similarly, our data on covariates are very complete due to chart review and validation, and time-varying anticoagulant use is based on detailed prescription fill records. The PA questionnaire

administered in the TI covers a wide range of activities with moderate or vigorous MET intensity levels and included an option to report additional activities. Previous research on incident VTE and MVPA has not commonly looked at participation in specific intensity MVPA separately from total MVPA; our approach may be applicable to evaluating both incident and recurrent VTE.[5]

Our study also has various limitations. Recall bias is probable, given that the median time between the incident VTE and the TI was about 2 years; however, it is likely that individuals' memories of behaviors just prior to their incident VTE are stronger due to the adverse health event, so recall of this period may be better than typical. Nearly 32% of individuals who experienced an incident VTE died prior to the TI and were not included in our study because they have missing MVPA data. Notably, among all adults that did not or could not complete the TI, there was a greater prevalence of cancer (38.2%) and hospitalization (30.5%) compared to individuals who did complete the TI (cancer = 10.2%, hospitalization = 20.0%). The cohort in our study therefore appears to have lower prevalence of provoking factors and be generally healthier than the general population of adults with incident VTE. Among those contacted for the TI there was an 81% interview response rate, which may introduce further bias if those who responded are characteristically different from those who did not.

Because we condition our population based on having experienced an incident VTE, index event (collider) bias is a likely concern and prevents us from drawing causal conclusions.[34] Greater amounts of MVPA may protect individuals from risk factors we did not account for, so without perfect control for confounding our estimate may be biased towards the null and may not represent accurate risk in recurrence prediction models.[34] Further, we had no measure of sedentary behavior in our cohort. While there is some evidence of a tradeoff between light PA and sedentary behavior, our exposure does not include light PA.[12] Sedentary behavior appears to be distinct from MVPA behavior, and one many not necessarily influence the other, so sedentary behavior may best be treated as a separate exposure.[12]

While the PA questionnaire used in HVH is much more thorough than many available self-report instruments, it lacks elements that could improve our measures of true PA intensity. Additional measures such as heart rate or the walk-and-talk test [29], or specific questions of intensity within each activity (i.e. walking for exercise, walking uphill, or casual walking) could allow better ascertainment of intensity. The TI also lacked questions regarding light intensity PA, so we cannot further classify individuals with no MVPA by participation in light PA or not. Finally, without a more detailed measure of intensity for individuals, the cutoff between moderate PA and vigorous PA may be too crude and likely misclassifies some reported PA within intensities. By looking at any MVPA in our primary analyses though, we account for this. Future studies that measure MVPA after an incident VTE and evaluate this in relation to VTE recurrence could help inform guidance regarding MVPA after an incident VTE event.

Conclusion

In a cohort of adults with an incident VTE, there is no evidence that energy expenditure in any MVPA is associated with risk of recurrent VTE for PA prior to the index event. Moderate and vigorous intensities of PA, separately, also had no evidence of association with risk of recurrent VTE. Obesity may modify the relationship between vigorous PA and VTE recurrence risk.

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