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Physical Activity and Hemostatic and Inflammatory Variables in Elderly Men

S. Goya Wannamethee, PhD; Gordon D.O. Lowe, MD; Peter H. Whincup, FRCP; Ann Rumley, PhD; Mary Walker, MA; Lucy Lennon, BSc

Background—Physical activity is associated with lower risk of cardiovascular disease, but the mechanisms are uncertain. Hemostatic and inflammatory markers have been linked with risk of cardiovascular disease. We therefore examined the relationship between physical activity and hemostatic and inflammatory variables.

Methods and Results—In 1998 to 2000, 20 years after the initial screening of 7735 men 40 to 59 years old from general practices in 24 British towns, 4252 subjects (77% of available survivors, now 60 to 79 old) attended for reexamination. A fasting blood sample was available in 4088 men. All men on warfarin (n=134) and men with incomplete data on physical activity (n=144) were excluded, leaving 3810 men for analysis. Physical activity showed a significant and inverse dose-response relationship with fibrinogen, plasma and blood viscosity, platelet count, coagulation factors VIII and IX, von Willebrand factor, fibrin D-dimer, tissue plasminogen activator antigen, C-reactive protein, and white cell count, even after adjustment for possible confounders. The effects were similar in men with and without prevalent cardiovascular disease. No relationship was seen with activated partial thromboplastin time, activated protein C resistance, hematocrit, or factor VII. An examination of changes in physical activity between baseline and 20 years later showed that inactive men who took up at least light physical activity had levels of blood variables approaching those who remained at least lightly active. Those who became inactive showed levels more similar to those who remained inactive.

Conclusions—These data suggest that the benefit of physical activity on cardiovascular disease may be at least partly a result of effects on hemostasis and inflammation. (*Circulation*. 2002;105:1785-1790.)

Key Words: exercise ■ hemodynamics ■ inflammation

Regular physical activity in leisure time is associated with reduced risk of coronary heart disease (CHD), stroke, and cardiovascular mortality in middle age and older age, although the mechanisms are unclear.¹ Because physical activity has to be current and continuous to confer protection,² the benefit may be at least partly due to a short-term effect, possibly through influences on blood coagulation, fibrinolysis and platelet aggregation,^{3,4} viscosity,⁵ or inflammatory markers such as C-reactive protein (CRP).⁶ Prospective studies have linked several of these variables, including fibrinogen, CRP, white cell count, viscosity, coagulation factors VII and VIII, and fibrinolytic variables [tissue plasminogen activator (tPA), fibrin D-dimer] to the risk of CHD.⁷⁻¹⁰ Although there have been several reports on the effects of exercise on these blood variables, most of these studies have been carried out in trained athletes or under a training program or have looked at the acute, short-term effects of physical activity, which may differ from the effects of habitual exercise.^{3,4} Several population studies have re-

ported significant inverse relationships between physical activity and fibrinogen.^{3,11-15} Less is known about the influence of regular leisure-time physical activity in the general population on other variables, although inverse relationships have been reported for factor VII,¹⁴ factor VIII,¹⁵ tPA,¹⁶ fibrin D-dimer,⁵ plasma viscosity,^{5,17} and CRP.¹⁵ In this article, we examine the relationships between physical activity, viscosity, inflammatory markers (CRP and white cell count), and several hemostatic variables in a large population-based study of 4000 British men 60 to 79 years old.

Methods

Subjects

The British Regional Heart Study is a prospective study of cardiovascular disease (CVD) involving 7735 men 40 to 59 years old selected from the age-sex registers of 1 general practice in each of 24 British towns, who were screened between 1978 and 1980.¹⁸ Research nurses administered a standard questionnaire including questions on physical activity, smoking, and medical history. During follow-up, similar questionnaires were mailed to the men in 1983 to

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1985 (Q5), in 1992 (Q92), and again in 1996 (Q96). In 1998 to 2000, all surviving men, now 60 to 79 years old, were invited for a 20th-year follow-up examination, carried out in a local health center. All men completed a questionnaire (Q20) providing information on their medical history, smoking and drinking habits, physical activity, and occupation; they had a physical examination and provided a fasting blood sample. Of the 5565 surviving subjects, 4252 (77%) attended for examination; 4088 men had ≥ 1 measurement of hemostatic and inflammatory variables. We further excluded 134 men currently on warfarin (since 1997), leaving 3954 men. Nearly 30% of the men ($n=1148$) were on aspirin.

Hemostatic and Inflammatory Variables

Blood was anticoagulated with K₂-EDTA (1.5 mg/mL) for measurement of hematocrit, white cell count, and platelet count in an automated cell counter and plasma viscosity at 37°C in a semiautomated capillary viscometer (Coulter Electronics). Blood viscosity was calculated from hematocrit and plasma viscosity as previously described.¹⁹ Blood was also anticoagulated with 0.109 mol/L trisodium citrate (9:1 vol:vol) for measurement of clottable fibrinogen (Clauss method) as well as coagulation factors VII, VIII, and IX; activated partial thromboplastin time (aPTT); and activated protein C (APC) resistance²⁰ in an MDA-180 coagulometer (Organon Teknika). Plasma levels of tPA antigen and D-dimer were measured with ELISAs (Biopool AB), as was von Willebrand factor (vWF) antigen (DAKO). CRP was assayed by ultrasensitive nephelometry (Dade Behring).

Physical Activity

At initial screening (Q1) and at reexamination (Q20), the men were asked to indicate their usual pattern of physical activity, under the headings of regular walking or cycling, recreational activity, and sporting (vigorous) activity. Regular walking and cycling related to weekday journeys, which included travel to and from work. Recreational activity included gardening, pleasure walking, and do-it-yourself jobs. Sporting activity included running, golf, swimming, tennis, sailing, and digging. A physical activity (exercise) score was derived for each man on the basis of frequency and type (intensity) of the physical activity. Scores were assigned for each type of activity and duration on the basis of the intensity and energy demands of the activities reported.²¹ The total score for each man is not a measure of total time spent in physical activity but rather is a relative measure of how much physical activity has been carried out.

Physical Activity Index

The men were initially grouped into 6 broad categories based on their total score:

(1) inactive: score 0 to 2 ($n=417$); (2) occasional: score 3 to 5 ($n=884$); regular walking or recreational activity only; (3) light: score 6 to 8 ($n=715$); more frequent recreational activities, sporting exercise less than once a week, or regular walking plus some recreational activity; (4) moderate: score 9 to 12 ($n=545$); cycling, very frequent weekend recreational activities plus regular walking, or sporting activity once a week; (5) moderately vigorous: score 13 to 20 ($n=656$); sporting activity at least once a week or frequent cycling, plus frequent recreational activities or walking, or frequent sporting activities only; (6) vigorous: score ≥ 21 ($n=593$); very frequent sporting exercise or frequent sporting exercise plus other recreational activities. The use of the physical activity score was validated by use of heart rate and forced expiratory volume in 1 second (FEV₁) in men free of preexisting CHD. Mean heart rate and FEV₁ decreased significantly with increasing levels of physical activity even after adjustment for potential confounders. This is consistent with the original validation of the physical activity score derived at baseline by use of baseline heart rate and FEV₁.²¹ We have excluded 144 men who did not provide complete data on the physical activity questionnaire at Q92; thus, our report is based on 3810 men.

Men With Preexisting CVD

The men were asked about a doctor's diagnosis of angina or heart attack (myocardial infarction or coronary thrombosis), heart failure, "other heart trouble," aortic aneurysm, claudication, deep vein thrombosis or pulmonary embolism, stroke, or diabetes. Twelve hundred forty-five men had 1 such diagnosis.

Cardiovascular Risk Factors

Smoking

From the combined information at screening and follow-up questionnaires, the men were classified into 5 smoking groups: (1) those who had never smoked, (2) ex-smokers since baseline, (3) smokers at baseline who gave up between screening and 1996, (4) smokers at baseline who gave up after 1996, ie, within the previous 4 years, and (5) current cigarette smokers. Nonsmokers include groups 1 through 4 combined.

Body Mass Index

Body mass index (BMI) (weight/height² in kg/m²) was calculated for each man at reexamination. Obesity is defined as BMI ≥ 28 kg/m², the upper fifth of the distribution of BMI in all men at screening.

Alcohol Intake

The men were asked about frequency of drinking (none, occasional or special occasion, weekend, and daily drinkers) and were asked to provide estimated weekly intake. On the combined information on frequency of drinking and reported weekly estimate, the men were classified into 5 groups: none, occasional/special occasions, and 3 groups of regular drinkers (light, 1 to 15 U/wk; moderate, 16 to 41 U/wk; and heavy, ≥ 42 U/wk), with a unit being 8 to 10 grams.²²

Statistical Analysis

The distributions of white cell count, CRP, fibrin D-dimer, and aPTT were highly skewed, and log transformation was used. ANCOVA was used to obtain adjusted mean levels for the 6 physical activity groups. Standardized differences in Table 1 were calculated as the difference in mean divided by the SD. Logistic regression was used to assess the odds of having elevated levels of the hemostatic and inflammatory variables, adjusted for confounders including age, BMI, smoking, alcohol intake, preexisting CVD, and month of examination. Tests for linear trend for physical activity were assessed by assigning quantitative values (1–6) for the 6 groups of physical activity and fitting physical activity as a continuous variable. Age and BMI were fitted as continuous variables; alcohol, smoking, and month of examination as categorical variables; and preexisting CVD as a dichotomous variable (yes/no).

Results

In age-adjusted analyses, physical activity was significantly and inversely associated with several hemostatic and inflammatory variables, including hematocrit, white cell count, platelet count, CRP, plasma viscosity, blood viscosity, clottable fibrinogen, factors VIII and IX, vWF, tPA, D-dimer, aPTT, and APC ratio. No association was seen with factor VII. Except for aPTT, the inverse associations with physical activity persisted after adjustment for age, BMI, smoking, alcohol, preexisting CVD, and month of screening (Table 1). For comparative purposes, standardized differences in mean (see Methods) were calculated to compare the strength of association between physical activity and the hemostatic and inflammatory factors. Of the factors shown to be independently associated with physical activity, the strongest associations were seen for CRP and plasma viscosity and the weakest for vWF and blood viscosity.

Although the differences in absolute mean levels of the hemostatic and inflammatory factors between the physical

TABLE 1. Physical Activity and Adjusted Mean Levels of Hemostatic and Inflammatory Variables, Adjusted for Age, BMI, Smoking, Alcohol Intake, Preexisting CVD, and Month of Screening

	None (n=417)	Occasional (n=884)	Light (n=715)	Moderate (n=545)	Moderate to Vigorous (n=656)	Vigorous (n=593)	Test for Trend	% Change in Mean	Standardized Difference (Vigorous vs None)
White cell count, 10 ⁹ /L*	7.02	7.01	6.79	6.82	6.74	6.55	§	6.7	0.27
Platelet count, 10 ⁹ /L	244.5	239.6	236.7	230.9	230.9	231.0	§	5.5	0.21
CRP, mg/L*	2.29	1.80	1.73	1.68	1.43	1.54	§	32.8	0.36
Plasma viscosity, mPa · s	1.307	1.292	1.285	1.278	1.28	1.271	§	2.8	0.35
Blood viscosity, mPa · s	3.40	3.41	3.40	3.38	3.39	3.37	†	0.9	0.10
Fibrinogen, g/L	3.40	3.28	3.26	3.24	3.21	3.17	§	6.8	0.32
Factor VIII, IU/dL	138.1	133.1	131.3	130.1	129.8	130.4	§	5.6	0.21
Factor IX, IU/dL	138.0	134.5	133.2	131.2	132.6	130.3	§	5.6	0.36
vWF, IU/dL	148.1	139.6	135.6	138.8	135.6	138.8	‡	7.2	0.16
tPA, ng/mL	12.00	11.26	10.79	10.92	10.61	10.56	§	11.1	0.33
D-Dimer, ng/mL*	101.5	91.8	82.3	82.3	83.9	76.7	§	24.0	0.33
aPTT, sec*	30.6	30.7	30.5	30.8	30.4	30.4	NS	0.6	0.07

% change in mean indicates difference in mean levels (none–vigorous)/none.

*Geometric mean used.

†P<0.05; ‡P<0.001; §P<0.0001.

activity groups were small, the reduction in the odds (risk) of having high levels of these factors (defined as the top fifth of the distribution) was substantial (Table 2), even after adjustments for potential confounders. Factor VIII and vWF were highly correlated (r=0.69), and only the findings for factor VIII are shown, because physical activity showed stronger associations with factor VIII. Moderate levels of physical activity, which are associated with a significant reduction in CHD risk,²¹ were associated with an ≈40% reduction in having high levels of fibrinogen, plasma viscosity, factor VIII, factor IX, and D-dimer; an ≈30% reduction in having high tPA antigen; and a 20% reduction in having high blood viscosity.

We examined the relationship separately in men with and without preexisting CVD or diabetes. Men with preexisting CVD overall had significantly higher adjusted mean levels of fibrinogen, plasma viscosity, factor VIII, tPA, D-dimer, and CRP (but not factor IX or blood viscosity) than men without. The inverse relationship between physical activity and these factors in Table 1 was seen in both groups of men, and the

effects of physical activity on hemostatic and inflammatory variables were similar in the 2 groups (Figure).

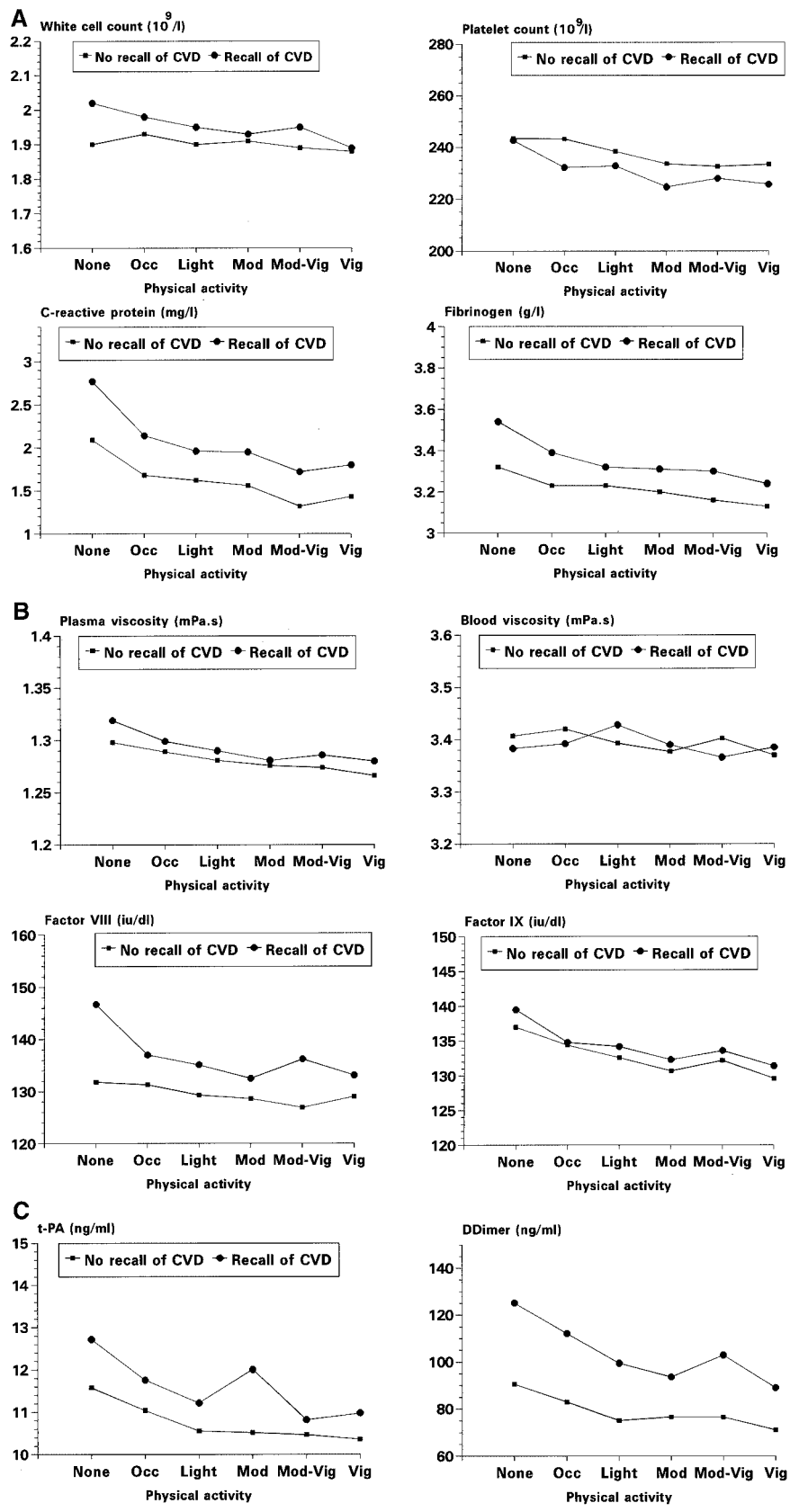
The relationships were similar in smokers and nonsmokers and in obese and nonobese subjects (data not shown).

Changes in Physical Activity

To assess whether physical activity has to be ongoing to have a beneficial effect, as well as the effects of taking up physical activity, we looked at change in physical activity between Q1 and Q20 and its influence on the hemostatic and inflammatory variables, excluding men with established CVD. The men were grouped into 4 groups (A through D) on the basis of their physical activity patterns at Q1 and Q20 (Table 3). All currently active men (irrespective of their past physical activity patterns) showed lower levels of these variables than those currently inactive. Those who had been at least lightly active at Q1 but were no longer active showed levels similar to those who had remained inactive. Those who became active showed levels similar to those who remained continuously active, particularly for tPA and D-dimer.

TABLE 2. Adjusted Relative Odds (CL) of Being in the Top Fifth of the Distribution of Hemostatic and Inflammatory Variables Compared With Those Reporting No Physical Activity, Adjusted for Age, BMI, Smoking, Alcohol Intake, Preexisting CVD, and Month of Screening

	None	Occasional	Light	Moderate	Moderate to Vigorous	Vigorous	P, Test for Trend
White cell count, ≥8.5 × 10 ⁹ /L	1.00	1.09 (0.84, 1.42)	0.84 (0.63, 1.11)	0.87 (0.64, 1.18)	0.86 (0.64, 1.15)	0.61 (0.44, 0.84)	0.0002
Platelet count, ≥279 10 ⁹ /L	1.00	1.00 (0.77, 1.32)	0.91 (0.68, 1.20)	0.72 (0.53, 0.99)	0.68 (0.50, 0.92)	0.66 (0.48, 0.91)	<0.0001
CRP, ≥4.27 mg/L	1.00	0.61 (0.47, 0.78)	0.64 (0.49, 0.83)	0.61 (0.45, 0.82)	0.37 (0.27, 0.51)	0.44 (0.32, 0.60)	<0.0001
Plasma viscosity, ≥1.34 mPa · s	1.00	0.92 (0.72, 1.18)	0.77 (0.59, 0.99)	0.61 (0.45, 0.82)	0.54 (0.40, 0.72)	0.43 (0.31, 0.59)	<0.0001
Blood viscosity, ≥3.625 mPa · s	1.00	1.04 (0.80, 1.36)	0.88 (0.66, 1.17)	0.81 (0.59, 1.10)	0.84 (0.62, 1.13)	0.82 (0.60, 1.11)	0.01
Fibrinogen, ≥3.76 g/L	1.00	0.66 (0.51, 0.85)	0.68 (0.52, 0.89)	0.57 (0.42, 0.78)	0.47 (0.42, 0.78)	0.46 (0.34, 0.63)	<0.0001
Factor VIII, ≥158 IU/dL	1.00	0.86 (0.67, 1.12)	0.76 (0.58, 1.00)	0.61 (0.44, 0.83)	0.62 (0.46, 0.83)	0.64 (0.47, 0.87)	0.0002
Factor IX, ≥151 IU/dL	1.00	0.86 (0.66, 1.12)	0.76 (0.58, 1.01)	0.57 (0.42, 0.78)	0.59 (0.44, 0.79)	0.54 (0.39, 0.74)	<0.0001
tPA, ≥14.3 ng/mL	1.00	0.74 (0.57, 0.96)	0.60 (0.45, 0.79)	0.72 (0.53, 0.98)	0.58 (0.43, 0.78)	0.64 (0.47, 0.87)	0.0003
D-Dimer, ≥149.9 ng/mL	1.00	0.75 (0.57, 0.97)	0.64 (0.48, 0.84)	0.61 (0.45, 0.84)	0.60 (0.45, 0.82)	0.47 (0.34, 0.64)	<0.0001



Physical activity and adjusted mean levels of hemostatic and inflammatory variables in men with and without preexisting CVD. Adjusted for age, BMI, smoking, alcohol intake, and month of screening.

TABLE 3. Changes in Physical Activity and Adjusted Mean Levels of Hemostatic and Inflammatory Variables Excluding Men With Preexisting Cardiovascular Disease, Adjusted for Age, BMI, Smoking, Alcohol, and Month of Screening

	Group A (n=361)	Group B (n=391)	Group C (n=432)	Group D (n=1361)	P, Test for Overall Difference Between Groups
White cell count, 10 ⁹ /L*	6.82	6.96	6.69	6.62	0.008
Platelet count, 10 ⁹ /L	242.9	244.0	231.8	234.5	0.007
CRP, mg/L*	1.73	1.73	1.57	1.42	0.0005
Plasma viscosity, mPa · s	1.289	1.293	1.279	1.273†	<0.0001
Blood viscosity, mPa · s	3.41	3.42	3.40	3.38	0.04
Fibrinogen, g/L	3.22	3.28	3.23	3.17	0.02
Factor VIII, IU/dL	131.0	131.7	129.4	128.1	NS
Factor IX, IU/dL	134.9	135.1	132.9	130.9†	0.0004
tPA, ng/mL	11.08	11.26	10.47†	10.47†	0.0007
D-Dimer, ng/mL*	84.8	84.8	73.7†	75.2†	0.002

Group A: inactive/occasionally active at Q1 and Q20.

Group B: at least lightly active at Q1; inactive/occasionally active at Q20.

Group C: inactive/occasionally active at Q1 but at least lightly active at Q20.

Group D: at least lightly active at Q1 and Q20.

*Geometric mean used.

† $P < 0.05$ vs group A.

Discussion

In this large study of men 60 to 79 years old, we observed that several hemostatic and inflammatory variables were dose-dependently and inversely associated with current physical activity. These relationships were similar in men with and without prevalent CVD, in smokers and nonsmokers, and in the obese and the nonobese.

These findings confirm and extend previous reports that physical activity is associated with lower levels of fibrinogen^{3,11–15} and viscosity,¹⁷ which are risk predictors for CHD.^{8,9} One possible mechanism through which regular exercise may reduce the risk of CHD and stroke may be reduction in blood viscosity, which increases blood flow and may therefore reduce the risk of clinical ischemia and/or thrombosis. Fibrinogen also increases thrombotic risk through promotion of platelet aggregation and fibrin formation.²³ There is little information on the effects of physical activity on platelets or blood coagulation.^{3,4} We observed significant inverse effects of physical activity on platelet count, vWF, coagulation factors VIII and IX, and fibrin D-dimer. No independent association was seen with aPTT or APC resistance. Although platelet count and aggregation do not appear to be risk predictors for CHD,¹⁹ prospective studies have associated increased levels of the factor VIII/vWF complex^{24,25} and increased levels of fibrin D-dimer¹⁰ with incident CHD. We could not confirm a previous report that factor VII was related to physical activity.¹⁴ Fibrinogen,²⁶ factor VIII,²⁷ and factor IX²⁸ are also related to venous thromboembolism. We therefore suggest that physical activity might have a protective effect against both arterial and venous thrombosis by reducing platelet count, cofactors in platelet adhesion/aggregation (hematocrit, fibrinogen, vWF), coagulation factors (VIII, IX), and fibrin turnover (as measured by fibrin D-dimer).

Physical activity may also reduce thrombotic risk by stimulating endogenous fibrinolysis,^{3,29} as expressed by high

levels of tPA activity.¹⁶ In normal subjects, plasma tPA activity is inhibited by an excess of plasminogen activator inhibitor type 1 (PAI-1), forming tPA/PAI-1 complexes, measured in plasma as tPA antigen. We observed that physical activity dose-dependently reduced plasma tPA antigen levels, probably by reducing plasma PAI-1 levels and hence tPA/PAI-1 complexes.^{7,16}

We observed dose-dependent inverse associations of physical activity with CRP and white cell count, consistent with a recent study.¹⁵ The present study therefore suggests that physical activity has anti-inflammatory effects as well as reducing viscosity and thrombotic tendency: these effects may be biologically linked.^{30,31}

The relationships of physical activity to blood variables were similar in men with and without prevalent CVD (Figure). Prospective studies show that the benefit of physical activity on cardiovascular outcome is seen in men both with and without CVD.^{32,33} Examination of changes in physical activity over 20 years and hemostatic and inflammatory variables 20 years later showed that those who were initially active and became inactive even in the absence of CVD showed levels similar to those in inactive men. In contrast, those who took up at least regular light activity showed levels approaching those of the continuously active men. These findings are consistent with our previous report showing lower all-cause mortality in those who take up or maintain physical activity in later life.³²

Factors such as plasma volume or triglycerides may confound the effects of physical activity on these blood variables. Plasma volume was not associated with physical activity in the present study, as measured by the hematocrit. A small but significant inverse relationship is seen between physical activity and triglycerides in the present study. Triglycerides showed little association with the parameters studied, however, apart from tPA, blood viscosity, plasma viscosity, and factor VII (which showed no association with physical

activity). The inverse relationship between physical activity and tPA, plasma viscosity, and blood viscosity persisted after additional adjustment for triglyceride.

In conclusion, regular leisure-time activity is associated with reductions in several hemostatic and inflammatory markers, including fibrinogen, viscosity, platelet count, white cell count, CRP, coagulation factors VIII and IX, vWF, and fibrinolytic variables (tPA, fibrin D-dimer). The benefit of physical activity on CVD may be at least partly a result of a short-term effect through these mechanisms. Further randomized studies are necessary to examine the effects of increased physical activity on these CVD risk predictors in men with and without prevalent CVD, as well as in women.

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