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Waist circumference and VO_{2max} are associated with metabolic and hemostatic risk in premenopausal nurses

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In 21 nurses (34.4±3.9 yr), VO_{2max}, physical activity, body composition and lifestyle parameters were measured to determine which of these characteristics are related to metabolic and hemostatic risk for cardiovascular disease. Physical activity was assessed with the 7-day recall interview. VO_{2max} was measured in a progressive and continuous treadmill test to volitional fatigue. Fasting insulin, total cholesterol, HDL-C, triglycerides, fibrinogen, tPA-act, tPA-ag, and PAI-1-ag were determined from fasting blood samples. Contrary to our expectation, there was no association of physical activity with any of these risk indicators. High VO_{2max} was associated with lower levels of insulin and fibrinogen. Regression analyses indicated that metabolic and hemostatic risk indicators, as measured in healthy premenopausal nurses, were mainly predicted by waist circumference and oral contraceptive use.

Over the past few decades, numerous studies have been published evaluating the relationship between physical activity and cardiovascular health, primarily in middle-aged and older men. The main outcome of these studies is that risk for the development of cardiovascular disease (CVD) seems to be reduced in physically active individuals versus their sedentary counterparts (Berlin & Colditz 1990, Powell et al. 1987). Increased physical activity is thought to provide cardioprotection, amongst others, by modifying several metabolic and hemostatic cardiovascular risk indicators. More favorable plasma lipid and lipoprotein profiles (Durstine & Haskell 1994, Kokkinos et al. 1995, Wood et al. 1991) have been reported in physically active compared with inactive persons. Physical activity lowers fasting insulin levels (Seals et al. 1984), blood pressure (Fletcher et al. 1992, Kokkinos et al. 1994), plasma fibrinogen (DeSouza et al. 1997), and improves fibrinolytic function, as evidenced by lower tissue-type plasminogen activator antigen (tPA-ag) and plasminogen activator inhibitor type 1 antigen (PAI-1-ag) (Ferguson et al. 1987, Stevenson et al. 1995, Wheeler et al. 1986).

Largely the same beneficial effects have been attributed to aerobic fitness, defined as the maximal oxygen consumption (VO_{2max}). High fit subjects have a more favorable metabolic and hemostatic risk profile than low fit subjects (Kokkinos et al. 1995, Andersen & Haraldsdottir 1995, DeSouza et al. 1998, Gibbons et al. 1983, Szymanski et al. 1996). Although individual differences in VO_{2max} are partly determined by physical activity behavior, they may largely reflect genetic endowment (Malina & Bouchard 1989). Heritabilities of 51–78% have been reported for VO_{2max} (Bouchard et al. 1998, Fagard et al. 1991), and at least 80% of fitness was found not to be explained by physical activity (Katzmarzyk et al. 1998). It is unclear to what extent the beneficial effects of physical activity and high aerobic fitness are overlapping (Andersen 1995). If they are independent, these effects could be additive or even synergistic.

To complicate matters, low levels of physical activity and aerobic fitness are usually associated with high levels of total body and abdominal fat (Wood et al. 1991, Andersen et al. 1998, Jette et al. 1992). At the same time, obese subjects are known to have an unfavorable metabolic and hemostatic profile, that may in part be a consequence of abdominal fat itself and the underlying insulin resistance (Lindahl et al. 1996). Therefore, body composition may be an overlapping factor underlying part of the associations of physical activity and aerobic fitness with CVD risk indicators.

The majority of the studies on physical activity and aerobic fitness have been conducted in men. However, CVD is not only the leading cause of death in men, but also in women (LaCroix 1995). The effects of aerobic fitness and physical activity on metabolic and hemostatic risk indicators in women have been seldom studied, and the findings have been equivocal

(Powell et al. 1987). In addition, most of the studies measured heterogeneous populations of both postmenopausal and premenopausal women or failed to take oral contraceptive use (OC-use) or stage in the menstrual cycle into account (Kokkinos et al. 1995, Andersen & Haraldsdottir 1995, DeSouza et al. 1998, Gibbons et al. 1983). The present study examined the relationship between directly measured $VO_{2max,}$ body composition, physical activity and metabolic and hemostatic risk indicators in healthy female nurses. OC-use was used as a covariate in all analyses. It was hypothesized that high levels of physical activity and aerobic fitness and low levels of body fat are independently associated with a more favorable metabolic and hemostatic risk profile.

Material and methods

Subjects

Twenty-one female nurses participated in this study (mean age 34.4 yr; SD=3.9). Subjects were randomly selected from a larger sample (n=159) of participants in an investigation of the effects of work stress on risk indicators of cardiovascular disease in female nurses. All of them were working on the same shift in the same hospital in the city of Amsterdam. Only healthy subjects, who were not receiving treatment or taking medication for hypertension, cerebrovascular disease, hyperlipidemia and/or diabetes mellitus, were included. Among the subjects were five cigarette smokers (maximum of 15 cigarettes a day). Subjects were briefed as to the nature, purposes and risks of the study. Those electing to participate gave their written informed consent. The study was approved by the Ethics Committee of the Vrije Universiteit of Amsterdam.

Procedure

Blood samples were collected at the workplace before starting an early shift between 7:00 and 7:30 a.m. Blood samples were drawn on two days of the same early shift. The first sample was taken on the first day of the early shift, the second sample on the third day of that same shift. Subjects were requested to fast and refrain from use of alcohol, coffee and tea after 11:00 p.m. the preceding night and to refrain from moderate or severe physical activity the preceding day. The blood was drawn from the arm in an upright sitting position after at least 15 min rest. The vacutainer blood withdrawal system was used for collecting the blood samples. Measured parameters were: fasting insulin, total cholesterol (TC), high-density lipoprotein (HDL-C), triglycerides (TG), fibrinogen, tissue-type plasminogen activator activity (tPA-act), tissue-type plasminogen activator antigen (tPA-ag), and plasminogen activator inhibitor type I antigen (PAI-1-ag). Blood pressure was measured twice by a calibrated SpaceLabs 90207 ambulatory blood pressure monitor (SpaceLabs Medical, Redmond, USA) after 10 min quiet resting.

Blood handling and biochemical assays

Blood withdrawal was according to the Standardized European Concerted Action on Thrombosis (ECAT) assay procedures (Kluft & Meijer 1996, Walker 1992). Blood was drawn by venipuncture of the antecubital vein, while the subject was seated, and sampled in six different vacutainers in the following order: serum (3 ml), serum with clot-activator (5 ml), stabilyte (5 ml), citrate (5 ml), EDTA (3 ml), NaF (2 ml). For determination of TC, TG and HDL-C, the serum with clot-activator was used. Blood was allowed to clot for minimal 30 min and maximal 2 h at room temperature. Serum was separated by centrifugation at 2000×g for 20 min at 4°C. Lipid determinations were performed on the same day using the Vitros 250 Clinical Chemistry analyzer (Johnson & Johnson, Rochester, USA) with Vitros clinical chemistry slides for TC and TG. High-density cholesterol (HDL) was measured in serum after a precipitation step with HDL-C precipitant (Boehringer Mannheim, Mannheim, Germany). All lipid results are given as millimoles per liter ($mmol \cdot l^{-1}$).

Fasting insulin ($pmol \cdot l^{-1}$) was measured with an immunoradiometricassay kit (Medgenix Diagnostics Fleurus, Belgium) by means of the serum-tube. Blood had to clot for minimal 60 min at room temperature. Serum was separated by centrifugation at 2000×g for 20 min at 4°C. Aliquots of serum were stored at −20°C. Values were multipled by 0.139 to convert fasting insulin into milliunits per liter ($mU \cdot l^{-1}$).

Stabilyte blood was collected for the determination of tPA-act. Citrated blood was collected for the determination of PAI-1-ag, tPA-ag and fibrinogen. Immediately after collection, the tubes were put in melting ice and centrifugated within 60 min (2000×g, 20 min at 4°C). Aliquots of plasma were snap-frozen immediately using solid carbon dioxide and stored at −80°C. tPA-act was measured using the bio-functional immunosorbent assay Chromolize™ tPA (Biopool, Umeå, Sweden). Results are expressed in International Units per milliliter ($IU \cdot ml^{-1}$). PAI-1-ag was measured using the enzyme immunoassay Innotest PAI-1 (Innogenetics, Zwijndrecht, Belgium). Results are expressed in nanograms per milliliter ($ng \cdot ml^{-1}$). t-PA antigen was measured using the enzyme immunoassay Imulyse™ tPA (Biopool, Uneå, Sweden). Results are expressed in nanograms per milliliter ($ng \cdot ml^{-1}$). Fibrinogen was measured using the STA coagulation analyzer (STAGO, Asnières, France) and the STA Fibrinogen kit (Boehringer Mannheim, Mannheim, Germany). The results are expressed in grams per liter ($g \cdot l^{-1}$).

The intra-assay and inter-assay coefficient of variation were less then: 5.0% and 7.0% for fasting insulin, 4.0% and 6.0% for TC, 3.5% and 5.0% for HDL, 3.0% and 5.0% for TG, 7.5% and 10% for tPA act, 10% and 10% for PAI-1-ag, 10% and 12% for tPA-ag, 5% and 7% for fibrinogen. For each of the blood parameters, all 42 blood samples were analyzed in the same batch. Moreover, the blood samples, drawn from the same subjects on repeated blood withdrawal occasions, were analyzed simultaneously on the same plate. No sample had been stored for more than 7 months.

Laboratory testing

Preceding exercise testing, a detailed medical history was taken by interview. The subjects were asked about their age, medication, use of oral contraceptives, stage in the menstrual cycle, smoking habits, and alcohol consumption. Current smoking habits were assessed by self-report as number of cigarettes smoked per day, but the variable was recoded into smokers and nonsmokers in the statistical analyses. The average weekly alcohol intake was assessed by the number of glasses consumed per week. Assessment of the subject's physical activity pattern during a (normal) week ($kJ \cdot kg^{-1} \cdot d^{-1}$) was obtained by a Dutch modified version of the 7-day activity recall interview (Blair et al. 1985), as used by De Geus et al. (1993). Anthropometric measurements taken included body height, body weight, body mass index (BMI), waist and hip circumference. The measurements were taken while the subjects were wearing only light clothing. Body height was measured to the nearest centimeter, with subjects standing on a hard surface against a wall, using a square and tape measure fixed to the wall. Body weight was measured to within 100 g using a calibrated digital scale. BMI was calculated as the weight in kilograms divided by the square of height in meters. Waist circumference was measured at the

end of a normal expiration. A measuring tape was positioned at the level of noticeable waist narrowing with the subject standing erect. Hip circumference was measured with the tape positioned at the level of the symphysis pubis and the greatest gluteal protuberance. Measurements were recorded to the nearest 0.5 cm. The waist and hip circumference were used to compute the WHR (waist circumference/hip circumference) as an estimate of abdominal fat distribution.

Maximal oxygen consumption (VO_{2max}) was measured by a progressive and continuous test to volitional fatigue on a motorized treadmill (Quinton model 65, Seattle, USA). The subjects were instructed not to eat a large meal for at least 3 h preceding the test and to refrain from moderate or severe exercise in the 24-h period preceding the test. Subjects were fitted with a short-range radiotelemeter (Sport Tester PE 3000, Finland) for heart rate measurements. After familiarization with the laboratory environment and testing procedures, the test began with a 5-min warm-up at 0% inclination during which the speed was increased gradually to the protocol's respective running speed. The subjects were instructed to select a speed that felt comfortable and would allow a maximal effort within 15 min. The mean selected speed was in a range of 8–10 $km \cdot h^{-1}$ and this speed was maintained throughout the test. Throughout the test, the inclination was raised 2.5% every 3 min until volitional fatigue was reached. Subjects were motivated verbally to continue as long as possible until they could no longer continue running at the indicated speed. Subjects were not allowed to use the handrails. Respiratory measurements were obtained using an Oxycon Spirometer (Mijnhardt, The Netherlands), which was calibrated against two gas mixtures before each test. Oxygen uptake (VO_2), carbon dioxide concentrations (VCO_2), and the respiratory exchange ratio (RER) were computed and updated every 30 s of the test. Even though all subjects were encouraged to run to exhaustion, the attainment of VO_{2max} was accepted only when all 3 of the following criteria were met: (1) a plateau of VO_2 with increasing work rate, (2) a respiratory exchange ratio of 1.0 or higher, and (3) a heart rate within 10 beats per minute of age-predicted maximum heart rate.

Statistical analysis

Pearson correlation coefficients and multiple stepwise regression analyses (SPSSwin version 7.5) were used for statistical evaluations. In the multiple regression models, fasting insulin, TC, HDL-C, TG, fibrinogen, tPA-act, tPA-ag, PAI-1-ag, systolic blood pressure and diastolic blood pressure were used as dependent variables. VO_{2max}, physical activity, body composition, age, alcohol use, smoking habits and OC-use were used as independent variables. The $P<0.05$ level of significance was applied to all tests.

Results

All data were checked with regard to frequency distribution. Since fasting insulin and PAI-1-ag were not normally distributed in this sample, these variables were logarithmically transformed prior to analysis to normalize their skewed distribution. Mean values, standard deviations and ranges of anthropometrics, blood parameters, self-reported physical activity and VO_{2max} are presented in Table 1. For readability, the original untransformed values are given.

Table 2 shows Pearson's correlation coefficients among the blood parameters, age, OC-use, waist circumference and VO_{2max}. VO_{2max} was negatively associated with fasting insulin ($r=-0.56$, $P<0.000$) and fi-

Table 1. Subject characteristics

Variable	Mean (n=21)	SD	Range
Age, years	34.4	3.9	29–41
Body composition			
Height, cm	170.2	4.6	162–180
Weight, kg	70.8	13.5	51.1–108.8
Waist circumference, cm	76.6	11.2	65.0–110.0
BMI, $kg \cdot m^{-2}$	24.43	4.61	19.31–38.39
WHR	0.78	0.03	0.71–0.87
Smokers, n (%)	5 (24)		
OC-use, n (%)	10 (48)		
Blood parameters			
Fasting insulin, $mU \cdot l^{-1}$	7.35	2.31	4.24–13.72
TC, $mmol \cdot l^{-1}$	4.73	0.99	3.34–7.24
Triglycerides, $mmol\ l^{-1}$	1.01	0.28	0.61–1.65
HDL-C, $mmol\ l^{-1}$	1.57	0.38	0.97–2.43
Fibrinogen, $g \cdot l^{-1}$	3.00	0.61	2.06–4.30
tPA-act, $IU \cdot ml^{-1}$	0.74	0.33	0.20–1.38
tPA-ag, $ng \cdot ml^{-1}$	4.67	2.07	1.98–9.21
PAI-1-ag, $ng \cdot ml^{-1}$	45.34	42.69	6.10–142.22
Cardiorespiratory fitness			
Resting systolic blood pressure, mmHg	125.52	11.87	105.00–153.00
Resting diastolic blood pressure, mmHg	74.02	12.82	50.00–95.50
VO_{2max}, $ml \cdot min^{-1} \cdot kg^{-1}$	35.0	4.4	27.2–42.9
Physcal activity, $kJ \cdot kg^{-1} \cdot d^{-1}$	200.4	21.0	163.6–252.5

BMI indicates body mass index; WHR, waist-hip ratio; OC-use, use of oral contraceptives; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; tPA-act, tissue-type plasminogen activatory activity; tPA-ag, tissue-type plasminogen activator antigen; PAI-1-ag, plasminogen activator inhibitor type 1 antigen.

Table 2. Pearson's correlation coefficients

Variable	Insulin†	TC	TG	HDL-C	Fibr	tPA-act	tPA-ag	PAI-1-ag†	SBP	DBP	PA	VO_{2max}	Age	Waist
Fasting insulin†	–													
TC		–												
Triglyceride			–											
HDL-C				–										
Fibrinogen	0.477*				–									
tPA-act			0.582**	0.523*		–								
tPA-ag						−0.538*	–							
PAI-1-ag†			−0.508*			−0.777**	0.823**	–						
Systolic BP									–					
Diastolic BP									0.452*	–				
Physical activity											–			
VO_{2max}	−0.563**				−0.575**							–		
Age					−0.469*								–	
Waist circumference	0.507*				0.707**	−0.594**	0.609**	0.557**				−0.655**		–
OC-use			0.571**	0.438*		0.646**	−0.562**	−0.583**					−0.457*	−0.587**

TC indicates total cholesterol; HDL-C, high-density lipoprotein cholesterol; tPA-act, tissue-type plasminogen activator activity; tPA-ag, tissue-type plasminogen activator antigen; PAI-1-ag, plasminogen activator inhibitor type 1 antigen; OC-use, use of oral contraceptives. *Correlation is significant at the 0.05 level, **correlation is significant at the 0.01 level, †logarithmically transformed.

brinogen ($r=-0.58$, $P<0.000$). No significant correlation was found between physical activity and any of the risk indicators or between physical activity and VO_{2max}. In addition, no significant correlation between stage in the menstrual cycle, smoking habits or alcohol use was found with any of the risk indicators. BMI ($r=0.93$, $P<0.000$) and WHR ($r=0.75$, $P<0.000$) showed high correlation with waist circumference and the risk indicators. However, of these three measures of body composition, waist circumference showed the highest correlations with the risk indicators. Only age, OC-use, waist circumference and VO_{2max} were retained for the regression analyses below.

Multiple regression analyses (stepwise) revealed that OC-use was the best predictor of HDL-C, TG, tPA-act and PAI-1-ag level, explaining respectively 19.2%, 32.6%, 41.7% and 34.0% of the variance (Table 3). Waist circumference and age explained 68.8% of the variance in plasma fibrinogen level. Waist circumference and VO_{2max} explained 50.1% of the variance in tPA-ag level. VO_{2max} was the best predictor of fasting insulin, explaining 31.7% of the variance in fasting insulin levels.

Discussion

The primary finding of this study is that the metabolic and hemostatic risk profile observed in a population of premenopausal healthy women appears to be predicted mainly by their waist circumference and OC-use. VO_{2max} was associated with fasting insulin and fibrinogen, but not independently from waist circumference. No associations were found between physical activity habits and any of the CVD risk indicators.

The metabolic and hemostatic risk indicators examined in the current study are known to belong to a multiple risk factor syndrome, referred to as syndrome X or the insulin resistance syndrome (Reaven 1994). This syndrome refers to a clustering of CVD risk indicators that has been observed primarily in middle-aged and older people. It includes hyperlipidemia, hyperinsulinemia and insulin resistance, excess abdominal fat and inadequate fibrinolysis. Although we examined a healthy population, the usual pattern of correlations between these risk indicators was evident. For instance, the relation between insulin levels and waist circumference, earlier observed in a larger survey of premenopausal women (Seidell et al. 1990), was confirmed. The significant relation in this study between tPA-act, an important stimulator of fibrinolysis, and the cardioprotective HDL-C repeats the finding of Szymanski et al. (1996). High correlations were found between waist circumference and indicators of the hemostatic system, again in line with other studies (DeSouza et al. 1998, Andersen et al. 1998, Siegbahn & Ruusuvaara 1988).

Surprisingly few studies have been done on VO_{2max}

Table 3. Multiple regression analyses (stepwise) of cardiovascular risk indicators

Variable	Predictor 1	Beta coefficient	*P*-value	Predictor 2	Beta coefficient	*P*-value	Total R^2
Fasting insulin	VO_{2max}	−0.563	0.008				0.371
TC*							
HDL-C	OC-use	0.438	0.047				0.192
Triglycerides	OC-use	0.571	0.007				0.326
Fribrinogen	Waist	0.685	0.000	Age	−0.434	0.004	0.688
tPA-act	OC-use	0.646	0.002				0.417
tPA-ag	Waist	0.922	0.001	VO_{2max}	0.477	0.044	0.501
PAI-1-ag	OC-use	−0.583	0.005				0.340
Systolic BP*							
Diastolic BP*							

TC indicates total cholesterol; HDL-C, high-density lipoprotein cholesterol; tPA-act, tissue-type plasminogen activator activity; tPA-ag, tissue-type plasminogen activator antigen; PAI-1-ag, plasminogen activator inhibitor type 1 antigen; OC-use, use of oral contraceptives; Waist, waist circumference. Total R^2 is cumulative variance explained by all significant predictors.
* No significant predictors.

and metabolic risk indicators in women. In studies on large groups of young women, TC (Andersen & Haraldsdottir 1995, McMurray et al. 1998) and TG (Andersen & Haraldsdottir 1995) were inversely associated with VO_{2max}. Two studies on both pre- and postmenopausal women, using treadmill time as a determinant of fitness levels, found a positive and significant relationship between HDL-C and fitness levels, and a negative relationship between TG and fitness levels, independent of age and weight (Kokkinos et al. 1995, Gibbons et al. 1983). In training studies in women (Duncan et al. 1991, Hardman et al. 1989, Hill et al. 1989), higher levels of HDL-C were found after a period of severe exercise training. Recent reviews in this area point to the importance of blood sampling during the same phase of the menstrual cycle and accounting for the use of oral contraceptives (Krummel et al. 1993, Taylor & Ward 1993). Correlational studies on lipids and aerobic fitness in women often failed to correct for oral contraceptive status (Kokkinos et al. 1995). The three training studies reporting a positive influence of exercise on HDL-C controlled for the phase of the menstrual cycle during blood sampling (Duncan et al. 1991, Hardman et al. 1989, Hill et al. 1989) but the number of subjects using oral contraceptives was not reported. In the current study, the menstrual status of the women had no impact on the risk indicators, but the results of our multiple regression analyses indicate that OC-use was responsible for a significant portion of the explained variance in the plasma levels of HDL-C and TG of healthy premenopausal women.

OC-use was also the main determinant of the fibrinolytic indicators. PAI-1-ag and tPA-ag levels correlated negatively with OC-use, whereas tPA-act was positively associated with OC-use. Elevated levels of plasma PAI-1-ag, tPA-ag and reduced tPA-act suggest lower fibrinolytic capacity and have been associated with myocardial reinfarction and CVD mortality (Jansson et al. 1991, Jansson et al. 1993). Our data suggest higher fibrinolytic capacity and reduced CVD risk in women using oral contraceptives. The currently available studies on fibrinolysis and OC-use are conflicting. Although higher tPA-act in plasma of OC-users has been detected before (Quehenberger 1993) and OC-use has been suggested to enhance tPA synthesis (Siegbahn & Ruusuvaara 1988), others have found no significant effects of OC-use on tPA-act (De Paz et al. 1995). For tPA-ag, OC users have been found to have either elevated levels (Siegbahn & Ruusuvaara 1988) or comparable levels to non-OC users (De Paz et al. 1995), both of which contrasts with the lower levels of tPA-ag observed in the present study. A reduction of plasma PAI-1-ag appears to be the most robust finding in OC-users. The inverse relationship between circulating PAI and OC-use found in the present study is in accordance with previous reports (Siegbahn & Ruusuvaara 1988, Quehenberger et al. 1993, De Paz et al. 1995). It has been assumed that the decrease of circulating PAI is due to the inhibitory effects of OC on PAI production and release from the endothelial cells (Siegbahn & Ruusuvaara 1988, Kluft & Lansink 1997).

Several epidemiological studies have reported that the excess body fat associated with obesity is a significant and independent risk indicator for CVD and related mortality (Coleman et al. 1992, Hubert et al. 1983). However, methods used to define obesity have often referred to excess weight rather than excess fat by measuring BMI. BMI does not provide a direct measure of adiposity or fatness but is a measure of proportional weight. Recent reports indicate that body fat distribution is more predictive of metabolic and cardiovascular diseases than BMI (Despres & Lamarche 1993, Despres et al. 1990). Most often the WHR has been used as an estimate of body fat distribution, but waist circumference by itself may be even more strongly associated with risk indicators (Andersen et al. 1998, Seidell et al. 1990, Ledoux et al.

1997). Seidell and colleagues (1990) reported that in women, waist circumference was significantly correlated with TC, HDL-C, TG, fasting insulin and diastolic blood pressure. Stevenson and co-workers (1995) showed that waist circumference was a better predictor of plasma levels of PAI-1-ag, tPA-ag, TG and lipoproteins than percent total body fat or WHR. In agreement with these studies, we found that waist circumference showed stronger associations than BMI and WHR with all risk indicators studied.

Both waist circumference and VO_{2max} were significantly correlated with plasma fibrinogen and fasting insulin level. After partialling out waist circumference, the primary determinant of fibrinogen, no additional effect of VO_{2max} on fibrinogen was found. In the same way, after partialling out VO_{2max}, the primary determinant of insulin, the correlation between waist circumference and insulin disappeared. Similar findings have been reported in a group of pre- and postmenopausal women (DeSouza et al. 1998). Insulin and fibrinogen are themselves correlated but the mechanism behind the correlation (Lindahl et al. 1996, Juhan-Vague et al. 1993) is poorly understood. Insulin resistance mediated free fatty acid release may be involved because this is accompanied by a rise in plasma fibrinogen levels (Pickart & Thaler 1980). Since it becomes increasingly apparent that adipocytes, besides being a fat storage cell, may synthesis and secrete a number of proteins e.g. fibrinogen (Loskutoff & Samad 1998), our data suggest that the favorable association between plasma fibrinogen levels and aerobic fitness may actually be mediated by a smaller amount of abdominal fat in highly fit subjects. Definite causality of aerobic fitness and body fat effects on insulin and fibrinogen remains to be established.

Neither physical activity status nor aerobic fitness level had any effect on PAI-1-ag, tPA-ag and tPA-act in the premenopausal women in this study. In accordance with our results, DeSouza et al. (1998) reported no differences in tPA-ag and tPA-act. However, they did find reduced levels of PAI-1-ag in physically active compared with sedentary premenopausal women, who also differed significantly in VO_{2max}. Based on their results, DeSouza et al. (1998) concluded that age-related changes in the fibrinolytic system may not be a primary effect of aging but that such changes may be due to reductions in physical activity or aerobic fitness and associated increases in body weight and fatness. This is in accordance with our findings: Waist circumference correlated significantly with the fibrinolytic variables and the multiple regression analysis revealed that waist circumference and VO_{2max} were the strongest correlates of tPA-ag, accounting for 50% of the variation.

No associations were found between physical activity habits and any of the CVD risk indicators. This is not in line with the results of previous studies in women (DeSouza et al. 1997, Stevenson et al. 1995, Andersen & Haraldsdottir 1995, McMurray et al. 1998, Duncan et al. 1991, Hardman et al. 1989, Hill et al. 1989). Because physical activity is a complex behavior that can be characterized in numerous ways, accurate assessment is difficult and intraindividual variability is large, even from week to week (Sallis et al. 1985). Thus, the size of the effect of physical activity on the risk indicators may have been too small to detect in our study, which had only a modest sample size. Alternatively, the contrast with previous studies may derive from 1) the choice of a homogeneous population, 2) standardization of hormone status. Previous studies always used heterogeneous populations, i.e. subjects differed in occupation and social economic status, and these differences may have been correlated with physical activity status. Secondly, sex hormone status has been poorly defined, either by not assessing OC-use or including both pre- and postmenopausal women in a single analysis (Kokkinos et al. 1995, Andersen & Haraldsdottir 1995, Gibbons et al. 1983, Duncan et al. 1991, Hardman et al. 1989, Hill et al. 1989). The present study was restricted to a homogeneous group of female nurses with known hormone status. In such a population, OC-use and waist circumference are the best predictors for metabolic and hemostatic risk indicators. We suggest that future research on the association of physical activity and aerobic fitness with cardiovascular risk should take occupational status, body composition and hormone status into account.

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Key words: maximal oxygen consumption; physical activity; cardiovascular risk; women; waist circumference; oral contraceptives.

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