Regular Physical Activity in Old Age

Effect on Coronary Heart Disease Risk Factors
and Well-Being

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Proefschrift

STELLINGEN

1. Regelmatig bewegen op oudere leeftijd is gunstig voor het cardiovasculaire risicoprofiel.
    (Dit proefschrift).

2. Een bewegingsprogramma verbetert de fysieke conditie en competentie van ouderen, en daarmee de kwaliteit van leven.
    (Dit proefschrift).

3. Sportbeoefening door ouderen beklijft beter wanneer uitgevoerd in groepsverband dan individueel.
    (Dit proefschrift).

4. Het evalueren van confouding gebeurt grondiger wanneer de gevonden associatie niet verklaarbaar is, dan wanneer deze wel verklaarbaar is.

5. Het doen van onderzoek bij ouderen wordt beloond met lessen in levenswijsheid.

6. Aangezien het risico op een trombotische aandoening verhoogd is bij ouderen als gevolg van de vergevorderde aderverkalking, is het gunstig beïnvloeden van de fibrinolyse vooral bij hen van belang voor de volksgezondheid.

7. Het verlengen van de tijd dat een voetgangersstoplicht op groen staat, kan het wandelen van ouderen in de stad stimuleren.

8. De voortdurende veranderingen in de Nederlandse spelling dwingen met name ouderen tot 'hersengymnastiek'.

9. Angst (bijv. BSE besmetting) is een belangrijker drijfveer voor het veranderen van leefstijl dan het potentiële effect op de volksgezondheid (bijv. lichamelijke activiteit).

10. De simultane stijging van de populariteit van de smartlap (*Witte rozen-De smartlap is de schaamte voorbij.* in: NRC 12 april 1997) en de daling van die van de hamlap (*Nederland in de greep van de varkenspest.* in: Varkens 1997;3:14-17) zijn een treffend voorbeeld van een niet-causale associatie.

11. Het door sommigen gesuggereerde verband tussen haarkleur en intelligentie van vrouwen, verdwijnt bij toenemende leeftijd.

12. Retorische vraag: 'And is not bodily habitus spoiled by rest and illness, but preserved for a long time by motion and exercise.' *(Socrates)*

Stellingen behorende bij het proefschrift
Regular Physical Activity in Old Age
Effect on Coronary Heart Disease Risk Factors and Well-Being
van Jantine Schuit

Wageningen, 16 juni 1997

Voor alle deelnemers
aan dit onderzoek

Abstract

Regular physical activity in old age: Effect on coronary heart disease risk factors and well-being
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Background. Regular physical activity is considered an important aspect of a healthy lifestyle. It may improve fitness, physical competence and may lower the risk of coronary heart disease (CHD). However, until now, data on the effects of regular exercise on CHD risk factors in elderly are limited, and there is a particular lack of data about the training effects on recently indicated risk factors, such as fibrinolytic and coagulation factors, and factors involved in the autonomic regulation of the heart.

Methods. We have conducted a randomised, controlled intervention study, which addressed the effect of a 6 months training programme on 'classical' and 'new' CHD risk factors and well-being in 229 (intervention:143 and control:86) apparently healthy, free-living elderly men and women (60-80 years).

Results. Physical fitness (maximal exercise capacity) improved significantly in subjects of the intervention group (mean increase 14.1 Watt , 95%CI: 10.1-18.1, +9%), compared to the controls. Among the classical CHD risk factors, only the reduction in serum triglyceride concentration in women was significant (-0.11 mmol/L, 95%CI: -0.22-0.0, -7%). Blood pressure, high- and low density lipoprotein and total serum cholesterol concentration changed in a favourable direction, but not significantly from the control group. No effect of training on body weight and fasting insulin concentration was found. Among the new risk factors, the concentration of tissue type plasminogen activator (t-PA), a fibrinolytic factor, was significantly increased (+0.07 IU/mL, 95%CI: 0.0-0.14,+11%) in subjects of the intervention group, while plasminogen activator inhibitor (PAI-1, inhibitor of fibrinolysis) was reduced, but not significantly different from the controls. These changes reflect an increase in fibrinolytic activity. However, fibrinogen concentration increased (+0.18 g/L 95%CI 0.04-0.32,+6%). In addition, heart rate variability was increased and heart-rate-adjusted-QT interval was reduced in subjects of the intervention group ($P<0.05$). Both changes probably represent increase in parasympathetic activity and a more favourable autonomic regulation of the heart. Finally, physical self-efficacy was significantly improved in the subjects of the intervention group. Symptoms of depression were reduced, but not significantly different from the controls.

Conclusion. Regular physical activity beneficially affected CHD risk factors, physical fitness and self-efficacy, which are important determinants of the quality of life and longevity in elderly. The magnitude of the benefits on CHD incidence remain unclear, since there is little information on the predictive value of the new risk factors in elderly. However, since elderly, in general, have advanced atherosclerosis and autonomic dysbalance, the improvements of these factors may be of particular importance in this age-group. In conclusion, our observations underline the importance of a public health policy aiming at stimulating regular physical activity in elderly people.

CONTENTS

CHAPTER 1

General Introduction

Regular physical activity is an important aspect of a healthy lifestyle. It increases aerobic capacity and strength (fitness), and may improve physical competence and quality of life. In elderly, it may prolong vitality by slowing down the ageing process, and increase longevity.[1] However, the proportion of inactive people increases with ageing. In the Dutch population, about 56% of elderly men and women above 65 is not physically active during leisure time, and only 17 % is physically active 3 times a week for more than 20 minutes, in walking, gardening or sports.[2]

Next to improvement of fitness and physical competence, regular activity may also reduce risk of chronic conditions, such as hypertension, type II diabetes and coronary heart disease (CHD).[3-5] Physical inactivity is recognised as an independent risk factor of CHD,[6] but it also affects CHD risk factors.[7-9] The potential beneficial role of exercise may be of particular importance in elderly, since they are generally less physically active than younger subjects. Moreover, elderly generally have more advanced atherosclerosis, and risk of myocardial infarction is greater than in middle-aged people.

Before addressing the rationale and design of the study, a brief introduction on the effects of physical activity on CHD (risk factors) is given, and the importance of risk factors at older age is discussed.

Physical activity and CHD

Evidence of an independent role of physical activity in the primary prevention of CHD has grown in recent years. One of the first epidemiological studies addressing the issue of physical activity was published by Morris *et al.*,[10] who observed a twofold-increased risk of CHD in sedentary postal carriers and bus conductors, as compared to postal carriers who walked their route. Later, after the 1970's, researchers started to investigate the association between leisure time physical activity and CHD. Especially studies performed by Paffenbarger *et al.*[11] and Blair *et al.*[12] have confirmed the findings of an elevated risk of CHD mortality among the least active subjects. In a meta-analysis, Berlin and Colditz[13] suggested a dose-response relationship between physical inactivity and risk of coronary heart disease, based on the fact that a stronger association

was observed when the high activity group was compared with a sedentary group than when it was compared with a moderately active group. Part of this meta-analysis was based on an earlier extensive review of Powell *et al.*,[7] who also reported a twofold-increased risk of heart attack in sedentary men as compared to men who were physically active in either jobs or recreational pursuits. This relative risk of CHD associated with physical activity is similar to that of smoking.

Physical activity and CHD risk factors

Many factors are involved in the development of CHD, e.g. high serum low density lipoprotein concentration, low serum high density lipoprotein concentration, high blood pressure, obesity and insulin resistance. Next to these, so-called classical risk factors, new CHD risk indicators have emerged. Recently, factors involved in the athero-thrombotic process (elevated plasma concentration of factor VII, plasminogen activator inhibitor-1, fibrinogen and homocysteine) were associated with increased incidence or recurrence of CHD.[14-19] Also, a reduced heart rate variability and a prolonged QT interval, characteristics derived from the electrocardiogram, were associated with cardiovascular disease, independent of other risk factors, in an apparently healthy population.[20,21] These recently established risk factors will be discussed later on in this chapter.

In several epidemiological studies, physical activity was associated with the classical, as well as some of the new risk factors. Reports show that regular physical activity may produce a more favourable lipoprotein profile, help to manage body weight, increase insulin sensitivity, fibrinolytic activity and parasympathetic tone, and lower blood coagulation and blood pressure.[3,7-9,22-24]

Importance of CHD risk factors at older age

The predictive value of CHD risk factors in elderly is less clear than among middle-aged subjects. Epidemiological studies that have investigated the role of classical risk factors in elderly, show inconsistent results,[25,26] although evidence

accumulates that hypercholesterolemia and hypertension have predictive value among the elderly.[27,28,29] The discrepancies observed in these studies may be partly explained by three aspects: (a) elderly are survivors, and may therefore be less susceptible to the effect of the risk factors, (b) the level of the risk factors may not reflect the level, these subjects had during most of their life; risk factors may change with ageing and consequently misclassification can occur, (c) with increasing age, there may be other risk factors that become more important, in addition to the classical risk factors.

Elderly, in general, have more advanced atherosclerosis and a higher prevalence of hypertension. Consequently, medical complications such as plaque rupture, which may result in thrombus formation and possibly occlusion of a coronary artery, are more likely to occur. Risk indicators, including fibrinogen and fibrinolytic factors are associated with thrombosis and the progression of atherosclerosis[30] and may therefore be of more significance in elderly[27] than in younger subjects. In addition, sympathetic activity increases with advancing age, which may indirectly lead to electrical instability of the heart. Improvement of the autonomic balance by increasing parasympathetic activity, may elevate the fibrillation threshold and prevent ventricular fibrillation, which may ultimately lead to sudden death. In the following, recently established CHD risk factors, which are likely to be associated with physical activity, are briefly introduced.

Fibrinogen

Fibrinogen is a large glycoprotein, mainly synthesised in hepatocytes, with a half life between 3 to 4 days. It is an acute phase reactant and its synthesis is stimulated by cytokines. Fibrinogen has several functions, but the main function is in the clotting process. Fibrinogen is transformed into fibrin (under influence of thrombin), which together with platelets forms blood clots (**Figure 1.1**). Fibrinogen also promotes the aggregation of activated platelets. Moreover, the amount of fibrinogen determines blood flow properties and fibrinogen and its split products are present in atherosclerotic plaques.[33] Elevated fibrinogen is associated with the incidence of CHD in men in various studies.[14] Although there is still controversy whether elevated levels may be a simple reflection of the extent of underlying atheroma, most researchers now consider fibrinogen a

major risk factor for CHD.[14,16,26] Plasma fibrinogen is raised by smoking[33] and with age[34,35] and it is higher after the menopause in women.[36] Cross-sectional studies give indications that fibrinogen is lower with increasing physical activity, but intervention studies among healthy middle aged and elderly show inconsistent results.[22,37,38]

Fibrinolytic factors

Fibrinolysis is the system that counteracts the thrombus formation and is therefore important in the pathophysiology of cardiovascular disease. Fibrinolytic activity is mainly regulated by tissue-type plasminogen activator (t-PA) and plasminogen activator Inhibitor type 1 (PAI-1), both glycoproteins. t-PA is synthesised by endothelial cells, whereas PAI-1 is synthesised by many cells, including endothelial cells and hepatocytes.[18] After synthesis, t-PA and PAI-1 are released in the plasma in active form, where they rapidly form an inactive reversible complex.[18,39] t-PA facilitates the conversion of plasminogen to plasmin, which degrades fibrin clots and removes fibrin from the vascular wall (**Figure 1.1**).

Figure 1.1. *Coagulation and fibrinolysis (simplified scheme).*

COAGULATION   FIBRINOLYSIS

various coagulation factors

↓

thrombin   t-PA

↓   ━━━ PAI-1

fibrinogen ➝ fibrin   ↓

↓ ◄─── plasmin ◄─── plasminogen

↓

fibrin degradation products
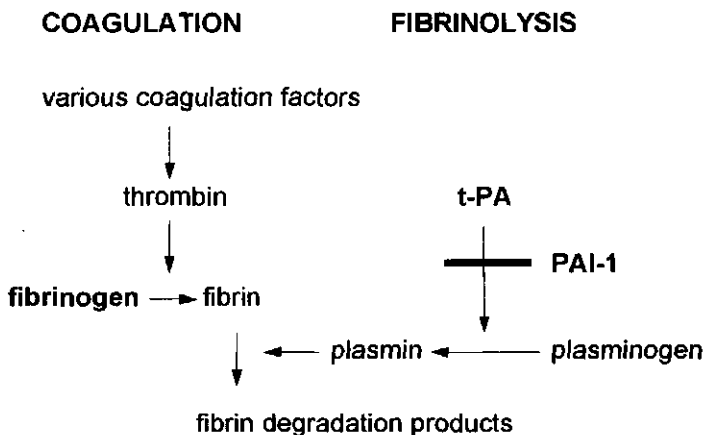
PAI-1 is a rapid inhibitor in this process by binding to t-PA. PAI-1 is increased in subjects with ischaemic heart disease, and elevated PAI-1 levels are a risk factor for myocardial reinfarction in young subjects.[15] Several studies show that PAI-1 antigen is positively associated with body mass index, serum triglyceride concentration, fasting insulin concentration and blood pressure, and inversely associated with physical activity.[23,33-35] t-PA activity correlates positively with physical activity.[19] Earlier studies have shown a positive association between physical activity and fibrinolytic activity.[40,41]

Heart rate variability

Heart rate variability (HRV) is the amount of spontaneous fluctuations around the mean heart rate, due to internal and external processes. It is used as a tool to investigate the sympathetic and parasympathetic function of the autonomic nervous system. Reduced HRV is associated with a two-to-three-fold increased risk of total mortality[42] and cardiac events[20] in healthy as well as myocardial infarction patients.[43] The biological mechanism underlying this association remains unclear. Probably, a reduced HRV reflects diminished parasympathetic activity. Sympathetic dominance in the autonomic cardiac control, may lead to electrical instability[44] and cause ventricular arrhythmias. Subjects with a high sympathetic drive more often have coronary atherosclerosis.[45] Next to being a contributor to the pathogenesis of CHD, low HRV may also reflect subclinical CHD. HRV diminishes with ageing, stress and smoking.[46] Most studies investigating the effect of physical activity on HRV have been performed in heart patients. These studies primarily show increase in HRV after training. However, studies performed in healthy middle aged and elderly subjects have come up with inconclusive results.[24,47]

QT interval

The QT interval is a characteristic of the electrocardiogram (**Figure 1.2**) and reflects the common duration of depolarisation and repolarisation of the ventricles. QT duration is prolonged by a heterogeneity in the cardiac repolarisation. This heterogeneity may be caused by (a) sympathetic imbalance (a predominance of the left sympathicus), particularly in the presence of high

sympathetic activity, or (b) from myocardial membrane properties that give rise to afterdepolarisation.
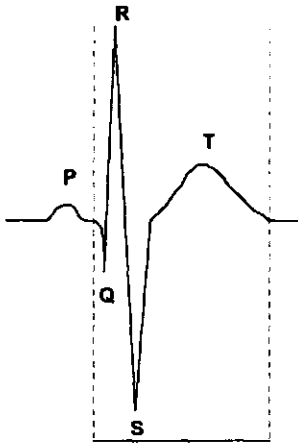
Some epidemiological studies have shown an independent association between QT-prolongation and risk of cardiovascular death, in particular sudden death in healthy people[21,48,49] and heart patients.[50] However, others did not find an association[51]. QT interval prolongs with ageing[52] and smoking.[53] Women have a longer QT interval than men[54] and QT is affected by medication[55] (e.g. anti arrhythmics, psychotropics, hypotensives and diuretics). Because physical activity may improve autonomic function, QT duration may also be affected. Until now there have been no reports on this topic.

Figure 1.2. *The QT interval.*

Rationale of the study

Until now, not many studies have investigated the effect of physical training on classical risk factors (blood pressure and serum lipids) in healthy elderly, and there is even greater paucity of data about the training effects on the recently indicated risk factors (elevated fibrinogen and PAI-1 antigen, low t-PA activity and HRV, and prolonged QT interval). In addition, there exists a major lack of data about physical activity and cardiovascular health in women.[4,7]

With the study presented in this thesis, we have tried to provide data to fill in some of these gaps. We have designed a randomised, controlled intervention study which addressed the effect of physical activity on both some classical as well as newly established risk factors, in healthy elderly men and women. Although it would be interesting and even preferable to study the effect of physical activity on CHD morbidity and mortality as well, it was unfeasible to study these in the present intervention study, because of problems related to the compliance and costs. Assuming that risk factors at

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older age still have a predictive value, intervention studies managing these risk factors seem appropriate.

Design of the study

Elderly subjects (aged between 60 and 80), living in Arnhem were approached via two general practitioners and were asked to participate in an intervention study on the effect of training on cardiovascular risk factors. In **Figure 1.3** the design of the study is depicted.

Figure 1.3. *Design of the intervention study*


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                              Study population
inclusion criteria:                  │
                              ┌───────┴───────┐
medical history               ▼               ▼
no MI or stroke in 2 yrs   volunteers      refusers
no IDDM, no heart             │
failure,no beta blockers  ◄─ selection │
medical examination:          │
normal resting ECG            ▼               ▼
no hypertension            eligible      not eligible
informed consent              │
                              ▼
        ┌───────────── randomization ─────────────┐
        ▼               ▼                          ▼
  bicycle group   all-round activity group   control group
  ┌──────────┐    ┌──────────────┐          ┌──────────────┐
  │6 months  │    │6 months      │          │6 months      │
  │4 times/week│  │3 times/week  │          │retain usual  │
  │30 minutes │   │45 minutes    │          │physical activity│
  │70% max. work load│ │aerobic training│   │pattern       │
  │individual activity│ │group activity│    └──────────────┘
  └──────────┘    └──────────────┘
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study parameters: weight, lipids, blood pressure, insulin, fibrinogen, t-PA, PAI-1, QT, HRV

After assuring eligibility (see inclusion criteria) and willingness to participate, subjects were randomly assigned to three groups: two intervention groups (an

exercise bicycle group and all-round activity group) and a control group. On average, randomisation results in comparability of all factors that may affect outcome of the study, even those factors that are not known to the investigator and which could therefore not be controlled for in observational studies. The purpose of the study was to recruit 100 subjects in both bicycle and control group and 50 subjects in the all-round activity group.

The intervention period was 6 months. This period was primarily based on results of previous physical activity intervention studies, investigating lipid changes, which reported effects only after 6 months. A longer period would probably have affected the compliance, which would lead to an underestimation of the effect attributable to the training programme.

A 'run-in' period, before the actual randomisation, to improve compliance during the intervention, did not seem feasible, since we believed that the 'run-in' ideally should include physical activity and this would have affected the outcome of the main study.

Adherence to the intervention protocol was stimulated by regular visits and phone calls. In the bicycle group, adherence was checked by a self-reporting cycling record. In the all-round activity group, the sports instructor kept a attendance list, in which the motivation and effort of the participant was reported as well.

We were interested in the physiological effects of 6 months' training and not in the feasibility of a training programme in elderly, therefore we used the 'intention to protocol' design, meaning that only those who stayed in the programme for 6 months were included in the analyses, regardless of the adherence to the exercise programmes during these months.

Outline of the thesis

In this thesis, the effects of a 6 months' training programme on classical and new CHD risk indicators in healthy elderly men and women are addressed. In Chapter 2, the effect of 6 months' training on lipids and body weight is reported. Chapter 3 to 5 describe the effect of training on the new risk indicators of CHD. Chapter 3 deals with the effect of training on fibrinolytic

factors and fibrinogen, Chapter 4 deals with training effects on QT interval and Chapter 5 describes training effects on HRV. The training effects on fibrinolysis, fibrinogen and HRV were studied in a subpopulation, for budgetary reasons. Although changes in risk factors may be very important in reducing risk of CHD, the subjective well-being of the elderly participating in the training programme is of equal importance. This is described in Chapter 6. In Chapter 7 we describe the validity of the physical activity questionnaire 'PASE' (Physical Activity Scale for the Elderly), which was used in our study. The validity of the PASE was assessed, using energy expenditure assessed by the doubly labelled water. Chapter 8 briefly addresses the long-term adherence of regular exercise among subjects of the intervention groups. In this chapter the two exercise protocols are compared. Finally, in Chapter 9, the results of the study are put in broader perspective. Methodological considerations of the study, as well as public health implications and suggestions for future research are reported in the general discussion.

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CHAPTER 2

The effect of 6 months training on weight, body fatness and serum lipids in apparently healthy Dutch elderly men and women

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ABSTRACT

The purpose of the study was to investigate the effect of a 6-months' training programme on changes in body weight and lipid concentrations, and their interrelationship, in a group of 229 elderly men and women, aged 60 to 80 years. The elderly were randomly assigned to a control group or a supervised aerobic training group, which exercised 3-4 times a week for 6 months.

During the intervention, no significant changes were observed in weight or body fatness in subjects of the training group. Serum HDL, LDL, total cholesterol and triglycerides changed in a favourable direction in elderly of the intervention group, but only triglyceride concentration in women was significantly reduced as compared to controls (intervention: mean -0.11 SE 0.06, control: mean 0.06 SE 0.06 mmol/L). Regression analysis showed that the intervention-control difference in lipid change was independent of changes in weight, body fat, energy intake or total fat intake. Both change in weight and body fat percentage were unrelated to change in lipid concentration.

In conclusion, regular physical exercise in an elderly population resulted in a significant reduction in triglycerides in women. Only a trend towards favourable changes in concentration in the other lipids was observed. Change in lipid concentration could not be attributed to change in weight or body fat.

INTRODUCTION

Advancing age is associated with profound changes in body composition. Body fat increases substantially,[1-5] while skeletal muscle mass decreases.[6] The age-associated increased fat mass accumulates mainly in the trunk.[7] Distribution of fat mass in the abdominal region has been associated with development of atherosclerosis, insulin resistance, hyperlipidemia, hypertension and the occurrence of cardiovascular disease and diabetes mellitus in men[8-12] and women.[8-11,13-15]

Increase in fat mass with ageing results mainly from declining physical activity (and a declining metabolic rate) coupled with an energy intake not matched to the declining need,[16-19] rather than being a consequence of the ageing process itself. Both cross-sectional[13,20] as well as training intervention studies[21-25] show a relationship between physical activity and body fat among elderly persons. It has been suggested that the reported beneficial effects of training on lipids,[26-30] like a reduction in triglycerides and increase of HDL concentration are merely a result of weight or fat loss, induced by training,[28,31-34] and not a weight-independent effect of training, which is proposed by others.[35,36] Also a change in energy percentage of fat intake as a consequence of higher energy intake may affect lipoprotein concentration.

Until now, not many intervention studies have been conducted among non-obese healthy elderly men and women, investigating the effect of training on plasma lipid concentration and body weight. Therefore, we studied the effect of regularly performed aerobic exercise on plasma lipids in a considerably large group of Dutch elderly men and women randomly assigned to an exercise group and a sedentary control group, without interfering with food intake. In addition, we investigated the role of body weight and body fat in this association.

SUBJECTS AND METHODS

Subjects
Eight hundred and twenty nine elderly, aged between 60 and 80, patients of two general practitioners and residents of Arnhem, the Netherlands, were asked to participate in an intervention study on the effect of training on cardiovascular

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risk factors. The general practitioners had selected these persons, using the following exclusion criteria: subjects with myocardial infarction or stroke in the past two years, insulin dependent diabetes mellitus, unstable angina pectoris, heart failure, and hypertension were not eligible.

One hundred and fifty two men and 166 women volunteered for participation (43% of the invited men and 35% of the invited women). All volunteers provided informed consent according to the guidelines of the Medical Ethical Committee of the Agricultural University Wageningen. Compared to refusers, volunteers were somewhat younger (men 68.5 ± 5.5 vs 71.5 ± 5.6 years, women 67.8 ± 5.4 vs 70.5 ± 5.4 years), and less often considered themselves inactive as compared to peers (men 49% vs 77%, women 48% vs 77%).

The volunteers were screened by a physical examination, which consisted of a resting supine and upright 12-lead electrocardiogram and blood pressure measurement. Subjects with no signs of present cardiovascular disease underwent a graded maximal exercise test. Subjects with ischaemic response (ST-depression > 2 mm) or those who were limited by heart failure during the exercise test were excluded from the study. In total 39 men (25.7%) and 50 women (30.1%) were excluded for medical reasons, which left us with a study population of 113 men and 116 women.

Randomisation and follow up

All 229 eligible subjects were randomly assigned to one of three protocols: an exercise bicycle group (48 men and 48 women), an all-round activity group (25 men and 22 women) or a control group (40 men and 46 women). Husbands and wives were randomised together. During the intervention 12 men and 19 women stopped with the bicycling programme (32%), 6 men and 5 women left the all-round activity group (23%) and 2 men and 2 women (5%) dropped out of the control group. Drop out in the bicycle group was mainly due to motivation problems (50%) and medical indication (40%). In the all-round activity group 7 elderly dropped out immediately after assignment, because they could not be present at the scheduled sport hours, due to other obligations, 4 elderly subjects stopped the programme because of medical reasons. Musculoskeletal problems were by far the most important medical reason for a premature

withdrawal (63%). Three subjects prematurely left the training programme because of cardiovascular disease. Subjects in the control group all left the study because of family circumstances.

Training

Subjects in the exercise bicycle group performed aerobic training during half a year, four times a week for 30 minutes. They exercised at a heart rate corresponding to 70% of their maximal exercise capacity, which was individually determined in the baseline maximal exercise test. The subjects received an bicycle ergometer at home which recorded their pulse rate. Adherence to bicycle protocols was captured in 3 ways; as a proportion of the target intensity, as an average percent of target days per week, and as a proportion of target time spent in every training session. The rate of adherence for each measurement was similar for men and women, namely; training intensity (97% and 98%), frequency (86% and 81%) and time spent (94% and 84%).

Subjects in the all-round activity group gathered 3 times a week for a 45 minutes' training session during half a year, led by an experienced sports instructor. The training consisted of aerobic exercise (ball games, exercise to music), callisthenics and flexibility exercises. The attendance in the all-round group was 72% for men and 81% for women.

Subjects in the control group were asked to maintain their habitual activities during the intervention period, but were not restricted from undertaking more physical activity, if desired.

Since both the bicycle and all round training protocols were similar with respect to intensity, duration and frequency and both programmes aimed at increasing aerobic capacity, for this report the groups were combined. Changes in the maximal exercise capacity and maximal oxygen consumption (determined in a sub-group, since there were no facilities available at the start of the study) were not different between the bicycle and all-round group. Therefore, comparable effects were expected on the study parameters. All participants were free to choose their own diet for the full period of the intervention.

Measurements

The measurements were performed identically before and after the intervention period.

Body mass index. Body height was measured (to the nearest 0.005 m) using a wall-mounted measuring tape. The subjects were standing without shoes. Body weight was measured on a calibrated weighing scale to the nearest 0.5 kg with the participants clothed in underwear.

Body fat. Body fat was estimated using the equation of Durnin and Womersley,[37] based on the sum of four skinfolds: triceps (halfway between the acromion and the olecranon), biceps (same level as triceps, directly above the centre of the cubital fossa), subscapula (about 2 cm below the tip of the scapula, at an angle of 45 to the lateral side of the body), suprailiac (just above the iliac crest, in the axillary line). In addition, we measured quadriceps (halfway between the iliac crest and the patella in a vertical line) and fibula (on the fibula at the level of the greatest circumference). Skinfolds were measured in triplicate at the left side of the body with a Harpenden skinfold calliper (Holtain/Tanner-Whitehouse; Holtain Ltd, Crymmych, UK). Pre and post measurements were performed by one person.

Serum lipids. A sample of fasting blood was drawn between 9.00 and 10.00 am, with subjects sitting down. Serum was obtained and stored at -80°C. Total cholesterol was analysed via enzymatic CHOD-PAP-Monotest method of Boehringer, triglycerides concentration via GPO-PAP method of Boehringer and high-density lipoprotein (HDL) was measured according to the method of Lopez Virella.[38] Low-density lipoprotein (LDL) was calculated using Friedewald formula.[39]

Maximal exercise capacity. The maximal work rate (Wmax) was measured on a bicycle ergometer. The initial work load was 60 Watt for men and 30 Watt for women. Every three minutes, work load was increased with 30 Watt. This protocol was applied in order to obtain a near steady state at each level and to perform cardiovascular screening simultaneously. The test was stopped when the subjects were exhausted or when there was a medical indication for premature halt. Maximal exercise capacity was determined through interpolation by summing up 10 Watt for every extra full minute of cycling on a certain work load.

Questionnaires on physical activity and food intake. Physical activity was measured with the Zutphen Study Questionnaire.[40] Energy- and fat intake were determined with a food frequency questionnaire.[41]

Data analysis

Mean lipid concentration, body weight, body fat, maximal exercise capacity and lifestyle factors at baseline were compared between control group and intervention group. The association at baseline between body weight and body fat, with lipid concentration was studied, using regression analysis. The effect of the exercise programme on lipid concentration, weight, body fat and skinfolds as well as on maximal exercise capacity, energy and fat intake was tested using Students t-test, comparing changes in intervention and control group. Paired t-test was used to study changes in lipid concentrations compared to baseline concentration within the groups. In addition, regression analysis with lipid change as dependent variate and intervention/control group (dummy) and confounders as independent variates was used to estimate the training effects independent of changes in energy intake, fat intake, weight or body fat during the intervention. Three men and 2 women of the intervention group had missing values on the pre intervention lipid measurement and were excluded. One woman and one man of the intervention group were excluded from all analyses, because of extreme dieting and weight loss. Therefore baseline data are presented for intervention group: 69 men and 67 women; control group: 40 men and 46 women. Intervention effects, studied in the subjects with complete follow up, included 51 men and 43 women of intervention group and 38 men and 44 women of control group. Three subjects were non fasting during the blood sampling and were excluded from data analysis regarding triglycerides. Data-analyses were performed with SAS 6.09 (Statistical Analyses System; SAS Institute Inc. Cary, USA).

RESULTS

Baseline results

Table 2.1 presents baseline characteristics of subjects in the control group and intervention groups.

Table 2.1. *Baseline characteristics of men and women in intervention and control group (mean ± sd)*

	MEN		WOMEN	
	Intervention (n = 69)	*control* (n = 40)	*intervention* (n = 67)	*control* (n = 46)
Age (years)	67.8 ± 5.3	69.5 ± 6.0	66.8 ± 5.1*	69.3 ± 5.2
Height (m)	177.6 ± 6.6	175.1 ± 5.9	164.0 ± 5.1	162.8 ± 6.1
Weight (kg)	80.1 ± 8.9	76.1 ± 11.4	68.0 ± 7.2*	64.2 ± 10.4
BMI (kg/m^2)	25.4 ± 2.5	25.0 ± 3.1	25.3 ± 2.9	24.2 ± 3.7
Body fat (%)	30.8 ± 4.5	29.7 ± 4.7	40.2 ± 3.7*	37.6 ± 4.9
TC[#] (mmol/L)	5.82 ± 1.10	5.93 ± 1.04	6.32 ± 1.02	6.31 ± 1.14
HDL (mmol/L)	1.07 ± 0.25	1.10 ± 0.27	1.22 ± 0.32	1.28 ± 0.32
LDL (mmol/L)	4.08 ± 0.97	4.14 ± 0.87	4.40 ± 0.93	4.42 ± 1.01
Triglycerides(mmol/L)	1.46 ± 0.81	1.51 ± 1.00	1.52 ± 0.68	1.31 ± 0.52
Energy intake (MJ/d)	10.20 ± 1.96	9.53 ± 1.69	8.36 ± 2.04	7.94 ± 2.05
Fat intake (en%)	39.8 ± 7.5	40.7 ± 6.3	40.9 ± 6.3*	38.1 ± 6.4
Wmax (Watt)	175 ± 42*	151 ± 42	119 ± 32	112 ± 29
Sport activity (min/wk)	104 ± 184	65 ± 123	68 ± 128	67 ± 129
Walking/bicycling (min/wk)	424 ± 331	395 ± 307	349 ± 287	338 ± 311
active in sport (%)	47.8	30.0	46.2	45.7
Smokers (%)	25.0	30.0	21.2	17.4
Alcohol drinkers (%)	79.4	87.5	60.6	52.2

* $P < 0.05$ difference between intervention and control, [#] total serum cholesterol

Women of the intervention group were on average slightly younger and had slightly higher levels of body fatness than controls at baseline, but the latter was not reflected in higher lipid concentrations. Men in the intervention group reported higher physical activity and had a higher mean baseline maximal

exercise capacity than the men in the control group. The remaining characteristics were not significantly different between intervention and control group. Nearly half of the population was already active in sport at baseline (46% of the women and 41% of the men). Subjects who were active in sport had a significantly higher mean serum HDL cholesterol (mean 1.23, SE 0.03 *vs* mean 1.12, SE 0.03, *P* < 0.01) and a significantly lower mean triglyceride concentration (mean 1.33, SE 0.06 *vs* mean 1.57, SE 0.07, *P* < 0.05).

Table 2.2 shows the association at baseline between serum lipids and body weight and body fat percentage. In men and women, body weight and body fat percentage were significantly associated with HDL (inversely) and triglycerides (p < 0.05), but not with LDL or total serum cholesterol. From all skinfolds, the truncal skinfolds (subscapularis and supra-iliacalis) and the bicipitalis were significantly associated with triglyceride concentration in both men and women and with HDL in women (*P* < 0.05) (data not shown).

Table 2.2. *Regression coefficients (SE) of baseline weight and body fat as independent and serum lipids (mmol/l) as dependent variate.*

	TC*	LDL	HDL	Triglycerides
Weight (kg)				
Men	0.08 ± 0.11	0.02 ± 0.10	-0.07 ± 0.03*	0.30 ± 0.11*
Women	0.05 ± 0.12	0.08 ± 0.10	-0.10 ± 0.03*	0.15 ± 0.06†
Body Fat (%)				
Men	0.04 ± 0.02‡	0.03 ± 0.02	-0.01 ± 0.005†	0.05 ± 0.02*
Women	-0.01 ± 0.02	-0.01 ± 0.02	-0.02 ± 0.01*	0.04 ± 0.01*

* *P* < 0.01, † *P* < 0.05, ‡ 0.05 < *P* < 0.10, # total serum cholesterol

Intervention outcomes

Table 2.3 shows mean 6-months changes in body weight, body fat, skinfolds, lipid concentration and maximal work rate in men and women of the intervention and control group.

Table 2.3. Mean change (±SEM) in lipid concentration, body fat and maximal exercise capacity over the intervention period.

| | INTERVENTION | | CONTROL | |
| | Men | Women | Men[s] | Women[s] |
	(n = 51)	(n = 43)	(n = 38)	(n = 44)
Change in:				
Weight (kg)	-0.48 ± 0.26	0.05 ± 0.35	-0.08 ± 0.38	-0.15 ± 0.26
Body Fat (%)	-0.11 ± 0.29	0.48 ± 0.25	-0.17 ± 0.31	0.71 ± 0.23
Supra iliaca (mm)	-1.56 ± 0.60	0.11 ± 0.83	-1.48 ± 0.84	1.49 ± 0.82
Ssf upper body +(mm)	1.41 ± 0.77	2.45 ± 0.84	0.70 ± 0.68	2.04 ± 0.82
Ssf lower body ¶(mm)	-1.48 ± 1.05	-3.01 ± 1.70	-2.01 ± 1.51	-2.29 ± 2.29
TC# (mmol/L)	-0.13 ± 0.09	-0.09 ± 0.11	-0.02 ± 0.13	-0.04 ± 0.10
HDL (mmol/L)	0.09 ± 0.03	0.09 ± 0.04	0.08 ± 0.04	0.12 ± 0.04
LDL (mmol/L)	-0.16 ± 0.07	-0.12 ± 0.10	-0.09 ± 0.10	-0.18 ± 0.08
Trigl (mmol/L)	-0.13 ± 0.07	-0.11 ± 0.06[†]	-0.01 ± 0.14	0.06 ± 0.06
Wmax (Watt)	15.7 ± 3.1†	9.8 ± 2.5*	4.4 ± 3.1	-6.6 ± 3.3
Sport activity (min/wk)	145.3 ± 24.2	118.3 ± 14.6	-13.8 ± 11.1	-16.4 ± 16.1
Walking/cycling (min/wk)	46.2 ± 50.4	-2.6 ± 39.4	-19.8 ± 55.1	-93.4 ± 52.9
Energy intake (MJ/d)	-0.21 ± 0.32	-0.46 ± 0.30[†]	-0.47 ± 0.26	0.37 ± 0.22
Fat intake (en%)	-0.5 ± 0.9	-2.1 ± 0.8	-0.3 ± 0.8	0.2 ± 0.9

*$P < 0.01$, † $P < 0.05$ T-test change in intervention group *vs* change in control group
[s]missing post lipid measurement (n = 1), + bicipitalis and tricipitalis, ¶ quadricipitalis and fibulicalis, # total serum cholesterol

Maximal exercise capacity (Wmax). The training programme resulted in a significant increase in maximal exercise capacity in both men (15.7 Watt, 9%) and women (9.8 Watt, 8%) of the intervention group as compared to controls.

Body weight and body fat. The subjects of the intervention group did not significantly reduce their weight or skinfolds as compared with the controls. The percentage of men who reduced their weight 1 kg or more, however, was higher in the intervention groups (45.5%) than in the control group (23.7%) (*P* = 0.03). In women this percentage was not significantly different, 36.4% and 38.6% respectively.

Serum lipids. Serum total cholesterol, HDL and LDL cholesterol and triglycerides changed in a favourable direction in both men and women of the intervention group, but only the change in triglycerides in women of the intervention group was significantly different from the change in the controls (**Table 2.3**).

Table 2.4. *Crude and adjusted difference (mean ± SE) in lipid concentration change (mmol/L) in intervention group as compared to the control group.*

	TC[#] change	HDL change	LDL change	Triglycerides change
MEN				
crude	-0.11 ± 0.15	0.02 ± 0.05	-0.07 ± 0.12	-0.12 ± 0.14
adjusted:				
body fat change	-0.10 ± 0.15	0.02 ± 0.05	-0.07 ± 0.12	-0.12 ± 0.14
weight change	-0.09 ± 0.15	0.02 ± 0.05	-0.06 ± 0.12	-0.11 ± 0.14
multivariate[†]	-0.07 ± 0.16	0.02 ± 0.05	-0.03 ± 0.13	-0.13 ± 0.15
WOMEN				
crude	-0.05 ± 0.14	-0.03 ± 0.05	0.06 ± 0.13	-0.17 ± 0.08*
adjusted:				
body fat change	-0.06 ± 0.15	-0.03 ± 0.06	0.04 ± 0.13	-0.16 ± 0.08*
weight change	-0.06 ± 0.15	-0.04 ± 0.06	0.05 ± 0.13	-0.17 ± 0.08*
multivariate[†]	-0.07 ± 0.16	-0.03 ± 0.06	0.03 ± 0.13	-0.16 ± 0.09

[†] adjusted for change in: weight (kg), energy intake MJ/day and total fat intake (g/day)

* *P* < 0.05

[#] total serum cholesterol

The mean difference in lipid change between intervention and control group, adjusted for change in weight or body fat percentage or change in weight, energy intake and total fat intake is shown in **Table 2.4**. In general, effect of training on lipid concentration was independent of changes in weight, body fat or food intake. Only difference in **LDL** concentration change between intervention and control group was reduced in men and women after multivariate adjustment. In women, the difference in total cholesterol change between intervention and control group became slightly more pronounced after adjustment, while in men the difference slightly decreased. Neither change in weight, or body fat percentage, nor change in food intake were significantly associated with a change in lipid concentration. In additional analyses, we excluded subjects using cholesterol lowering drugs (n = 5) from all analyses. Exclusion of these subjects, however, did not affect the outcome of the study.

DISCUSSION

In a group of apparently healthy Dutch men and women, 60 to 80 years old, we found that a community based supervised exercise programme resulted in small effects on body composition and blood lipids. A significant reduction in triglycerides was found in women, but not in men. Serum HDL, LDL and serum total cholesterol changed in a favourable direction in the intervention group, but changes were not significantly different from the changes in the control group. In this group of elderly subjects, training effects on lipids were not mediated by changes in body weight or total body fat, as was suggested earlier,[28,31-33] or by changes in energy or fat intake.

Change in maximal capacity (9%) was somewhat lower than reported in other studies. But since our group was not completely sedentary at baseline (shown by the relatively high baseline values of maximal exercise capacity), improvement in physical fitness was expected to be somewhat lower. Mean increase in time spent on sport activity indicates that subjects of the intervention group did not exchange their old sport activities for the new training programme. Also time spent on walking and bicycling did not decrease in the intervention group. We may therefore conclude that the intervention programme

was successfully followed and a considerable difference in activity with the control group was achieved.

Selective study population and drop out

Our study population consisted of healthy elderly subjects. Not only were subjects with cardiovascular disease excluded for reasons of protection, participants were also more active than refusers. The participating subjects had normal baseline lipid concentrations. Only 3% of the subjects had a serum total cholesterol concentration above 8 mmol/L. As previously reported, subjects with a raised lipid concentration tend to experience greater lipid alterations by exercise than subjects who have normal lipid concentration.[42] We therefore did not anticipate exceptional changes in lipid concentration and the observed small to moderate changes were probably more in the line of expectation. The health related selection limits generalizability of our results, but does not violate the validity of the study. A selective drop out during the intervention could, however, have biased our results. Of the 229 men and women enrolled in the intervention study, 46 dropped out (20%). Men who dropped out of the study had a lower baseline serum total cholesterol concentration (mean 5.36 mmol/L $p < 0.05$) and women who stopped prematurely gave themselves a lower score for health status, had more symptoms of depression and were less active in sport as compared to the subjects who completed the protocols ($p < 0.05$). Since we did not collect post-intervention blood samples of subjects who dropped out during the intervention period, we reported on the effects of training for those who were able and willing to complete the protocols. To investigate possible bias by selective drop out we have applied a general linear mixed model, which efficiently uses the full available data. This procedure estimates mean effects, corrected for non-random missing data, using maximum likelihood,[43] hereby minimising possible bias in the results due to selective drop out. The results of this procedure were very similar to the ones reported. In fact, significant differences were even more strongly significant, due to gain in efficiency. Therefore, we assume that drop out in our study has not confounded the results to a great extent.

Contamination of control group

An improvement in lifestyle (nutrition and physical activity) among subjects in the control group, as a result from participating in a physical activity intervention study can not be ruled out. Some of the participants were very disappointed in being assigned to the control group and although mean activity during intervention is slightly decreased in this group, it is still possible that some subjects may have increased their activity pattern. To investigate a possible contamination of the control group, we performed a regression analysis in which the effect of change in time spent on sport activity (hour/wk) in the past 6 months on lipid concentration and body weight was investigated, disregarding the intervention assignment. This way changes in activity, relative to baseline activity, for each subject in both control and intervention group could be distinguished. The regression showed that 1 hour increase in sport per week was associated with a significant decrease in serum total (men: -0.05 mmol/L, women -0.08 mmol/L) and LDL cholesterol (women -0.05 mmol/L) ($P<0.05$). Triglycerides were reduced in men (-0.03 mmol/L) and women (-0.01 mmol/L), but not significantly. Adjustment for change in weight (kg) or body fat percentage, change in food consumptions and initial sport activity in the model did not markedly affect the beta for change in sport activity in both men and women. These results varied slightly from the results of the intervention per se, especially regarding change in LDL and triglycerides concentration in women. Increase in sport activity of 1 hour per week in the past 6 months was associated with a reduction in weight of 0.15 kg/hour*wk^{-1} in men ($P=0.07$) and increase of 0.09 kg/hour*wk^{-1} in women ($P=0.40$). No associations were found in relation to body fat percentage.

Anthropometric measurements

In this study we used anthropometric measurements, which are relatively easy to perform, cheap and feasible in large field studies. However, the accuracy of predicting body fat from skinfolds is limited. Nearly all formulas underestimate the percentage body fat,[44] since they are based on young and middle-aged subjects. The best predictor of body fat content in elderly people using

anthropometric data seemed to be the equation of Durnin and Womersley[37], which was used in this study.[44] Although pre- and post-measurements were performed by one person, errors may have occurred in the estimated changes. However, assuming non differentiality, this would merely cause an underestimation of the interrelationships.

Other training studies

Randomised intervention studies investigating the effect of training on lipid concentration in healthy elderly subjects are far less in number than in middle aged subjects. Most training studies in elderly are conducted in male and obese subjects and little is known about training effects in non-obese healthy elderly women. The diversity of training protocols (which are often combined with diet intervention) and study populations makes it hard to compare our results with other studies. A few studies, however, need to be mentioned. Hughes *et al.*[33] investigated the effect of exercise in glucose-intolerant older subjects, while their weight was maintained. Like in our study, no significant effects on lipid indexes were observed. The authors concluded that this might be due to the lack of substantial weight loss. This assumption was, however, recently contradicted by data from Fox *et al.*,[45] who studied the effect of diet and exercise in moderately obese older women. Although body weight was significantly reduced in these women, no significant changes in blood lipid were observed. Katzel *et al.*[32] reported that obese men following an aerobic exercise training did not significantly reduce body weight and did not beneficially change their lipid levels, while men undergoing a weight loss intervention did. They also reported that elderly men had smaller declines in triglycerides and total serum cholesterol than middle aged had. King *et al.*[27] showed that elderly subjects, aged 50-65, increased HDL only after 2 years of regular moderate training. They hypothesised that the time frame needed to achieve HDL changes may be longer for elderly people than that reported previously for younger populations. Also the intensity of a training programme is suggested as an important determinant of lipid change.[29,30] It was proposed that mainly vigorous exercise training may enhance lipoprotein lipase activity (maybe through increase in insulin sensitivity), which accelerates turnover of triglycerides and enhances clearance of triglyceride rich lipoproteins. Training in our study consisted of

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exercise 3 to 4 times a week, for 40 minutes at about 70% of their maximal capacity. We believed that in this age group it was not feasible to make the training programme more vigorous or longer. This would probably have affected the compliance and increased drop out. This proved to be true for the partici- pants in the bicycle group, who found the programme hard to comply with, especially in the second half of the intervention period. Also the higher drop out caused by motivation problems in this group is in agreement with this.

A small decline in body weight and body fat percentage, as observed in our study, was also reported earlier. Also greater effects on body composition were found in men as compared to women. Women who follow a training programme seem to preserve their energy balance more strongly than men.[46,47] Westerterp et al.[46] proposed that women following a training programme may compensate for the increased energy expenditure with an increase in energy intake. This did not hold for the women of our study. In fact, women of the intervention group had significantly reduced their energy intake, according to the food frequency questionnaire. Probably, loss of fat mass coincided with increase in muscle mass, resulting in a stable body weight.

In summary, in healthy elderly subjects, following a 6 months community based intervention programme, a reduction in serum triglycerides (only in women significant) and a trend towards improvement in HDL and total cholesterol was observed (not statistically significant). Although small, the changes observed in our study may be important in relation to cardiovascular risk. Recently, Weijenberg et al.[48] showed that both total cholesterol and serum HDL are still important in predicting coronary heart disease in elderly men. They reported that a 0.26 mmol/L increase in HDL was associated with 20% reduction in the incidence of coronary heart disease, while a 1.00 mmol/L decrease in total serum cholesterol was associated with 30% reduction in mortality from coronary heart disease. Earlier, Zimetbaum et al.[49] also showed that an unfavourable lipoprotein profile at advanced age, still increased the risk of cardiovascular morbidity and mortality in both men and women.

It remains to be solved whether a change in lipid concentration at older age can still affect coronary risk. Apart from a possible preventive role in hyperlipidemia and obesity, physical activity has undisputed positive effects on

physical, social and emotional functioning. Especially in elderly people it seems important for maintaining health and independence.

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CHAPTER 3

The effect of strenuous exercise on fibrinogen and fibrinolytic factors in healthy elderly men and women

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ABSTRACT

The elevated incidence of thrombotic disease in elderly people may be associated with the increase in plasminogen activator inhibitor-1 (PAI-1) and fibrinogen with ageing. Cross-sectional studies report an inverse relation of PAI-1 and fibrinogen with physical activity, but training studies show inconsistent results.

In a controlled intervention study among elderly subjects (aged 60-80 years) we observed a moderate decrease in PAI-1 antigen (4%, -2.1 ± 2.4 ng/mL), a significant increase t-PA activity (11%, 0.07 ± 0.04 IU/mL) and an unexpected significant increase in fibrinogen (6%, 0.18 ± 0.07 g/L) in subjects following a 6 months intensive training programme as compared to controls. Reduction in PAI-1 antigen was significantly associated with a decrease in triglycerides ($\beta = 10.3$ ng/mL per 1 mmol/L, $P < 0.01$) and insulin ($\beta = 2.37$ ng/ml per 1 mU/L, $P = 0.07$). Increase in fibrinogen coincided with a rise in C-reactive protein ($P < 0.001$).

These data suggest that regular intensive activity may increase fibrinolytic activity in a moderate way, but may also cause chronically elevated plasma levels of acute phase proteins in elderly subjects.

INTRODUCTION

Atherosclerosis is a progressive condition of multifactorial origin. Of central importance in its pathogenesis are disorders of lipid metabolism. In the last few years, however, it has become evident that also haemostatic factors like fibrinogen and plasminogen activator inhibitor (PAI-1) may be critically involved in the process of atherogenesis and in subsequent thrombosis.[1,2] Elevated fibrinogen levels can affect atherogenesis by multiple processes, such as formation and growth of arteriosclerotic lesions,[3] proliferation and migration of smooth muscle cells,[4,5] promotion of aggregation of activated platelets[6] and deterioration of the blood flow properties.[7] PAI-1 plays a central role in fibrinolysis, by its inhibitory binding to tissue type plasminogen activator (t-PA). t-PA facilitates the conversion of plasminogen to plasmin, which degrades fibrin clots and removes fibrin from the vascular wall.

PAI-1 is considered to be linked to symptoms of the insulin resistance syndrome, such as overweight (central obesity), impaired glucose tolerance, elevated blood pressure, increased VLDL and triglycerides and decreased HDL.[8-10] It has even been hypothesised that an increased PAI-1 level could be the link between insulin resistance and coronary heart disease.[11] A recent study in mice suggested that adipose tissue itself may be an important contributor to the elevated PAI-1 plasma levels in obese. Both PAI-1 and fibrinogen levels increase with ageing,[12,13] in women especially after the menopause.[14] This rise may be one of the explanations of the elevated incidence of thrombotic disease in elderly persons.

Epidemiological cross-sectional studies have shown that active middle aged persons have lower fibrinogen and PAI-1 levels as compared to non-active persons.[15,17] However, the few reported intervention studies in healthy individuals[18-22], mainly in middle aged men, generally failed to show an effect of physical training on PAI-1 and fibrinogen.[19,21,23] One exercise intervention study showed significant and pronounced beneficial changes in both fibrinogen and fibrinolytic factors in healthy elderly men, but not in young men.[18] However, this study did not comprise a control group and the number of subjects was rather low.

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It remains unclear whether the observed association between physical activity with fibrinogen and fibrinolytic activity in cross-sectional studies was confounded by physical fitness and health. To further explore a possible beneficial role of exercise on coagulation and fibrinolysis in elderly people, we investigated the effect of a 6 months intensive training programme on fibrinogen, PAI-1 antigen and t-PA activity in a group of Dutch men and women, aged 60 to 80, randomly assigned to an intervention group and control group. In addition, we studied the relationship of levels of PAI-1, t-PA and fibrinogen with characteristics of the insulin resistance syndrome, both cross-sectionally and prospectively.

SUBJECTS AND METHODS

Subjects

829 independently living men and women, age 60 to 80, were requested via their family physician to participate in a controlled intervention study on the effect of exercise on cardiovascular risk factors. The general practitioners had selected these elderly subjects according to the following inclusion criteria; no myocardial infarction or stroke in the past two years, no insulin dependent diabetes mellitus, no unstable angina pectoris and no heart failure or hypertension. 152 men (44%) and 166 women (35%) volunteered to participate. Compared to refusers, participants were somewhat younger and less frequently considered themselves inactive as compared to their peers.

The volunteers were screened by a medical history questionnaire and a physical examination, which comprised resting electrocardiogram and blood pressure measurement. Subjects with no signs of cardiovascular disease underwent a graded maximal exercise test. Elderly people with signs of heart failure or an ST-depression of more than 2 mm during the exercise test were excluded from the study. As a results of the screening 39 men and 50 women were excluded, leaving a group of 113 men and 116 women. Laboratory measurements were performed in an aselect sample of 88 men and 94 women. Informed consent with the procedures was obtained from each subject before

entry into the study. The experimental protocol was approved by the Medical Ethics Committee of the Agricultural University Wageningen.

Randomisation and follow up

Men and women were randomly assigned to an exercise bicycle group (48 men and 48 women) and a control group (40 men and 46 women). We assigned slightly more subjects to the exercise bicycle group, because we expected a higher drop out in this group. During the intervention period 12 men and 19 women stopped with the training programme, mainly due to lack of motivation (50%) and medical reasons (40%). Drop out among the subjects of the control group (2 men and 2 women) was caused by family circumstances. Fibrinogen, PAI-1 antigen and t-PA activity were only determined in subjects who completed the protocols (74 men and 72 women), and there were missing values of 1 man and 1 woman, leaving us a study population of 73 men and 71 women.

Protocols and adherence

Subjects assigned to the exercise bicycle group received an exercise bike at home, which had a pulse recording facility. They trained four times a week for 30 minutes during 6 months. The intensity of the training was based on the maximal exercise test, which was administered at baseline. After a run-in period of 4 weeks, the intensity increased from a heart rate corresponding to 50% of their maximal work rate to a heart rate corresponding to 70% of their maximum. Adherence to the programme was checked with a cycling record. Adherence to intensity, frequency and duration of training of subjects who completed the programme was 97%, 86%, 94% and 98%, 81%, 84% for men and women respectively. Subjects in the control group were asked to maintain their habitual activities, but were not discouraged from undertaking more exercise.

Maximal exercise capacity

Every subject underwent a graded maximal exercise test on an ergocycle before and after the intervention period. The initial work load was 30 Watt for women and 60 Watt for men. Every three minutes the work load was increased with 30 Watt. The test was stopped when a subject was exhausted or when there was a medical indication for a premature halt. Maximal exercise capacity (Wmax) was determined through interpolation, by summing up 10 Watt for every extra full minute of cycling on a certain work load.

Anthropometry

Anthropometry was measured by the same person before and after intervention. Body weight was measured on a calibrated weighing scale with subjects wearing only light underwear. Body height was measured using a wall-mounted measuring tape, the subject standing without shoes. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

Assays

Before and after the intervention period blood samples were drawn from all participants without stasis between 9:00 and 10:00 AM after an overnight fast. The volunteers were at least for twenty minutes at rest before the puncturing of the ante-cubital vein. The subjects were required to abstain from smoking or drinking tea or coffee in the morning of the venepuncture. All subjects had refrained from alcohol consumption and strenuous activity the day before the sampling. The last training in subjects of the intervention group was minimal 2 days before the venepuncture. This way acute effects of training, smoking or alcohol consumption could be avoided.[24] The first 5 ml of blood were used for measuring lipids. Citrated blood, sampled for determination of fibrinogen, t-PA and PAI-1 was put on melting ice and centrifuged for 30 minutes at 1800 x g at 4° C within one hour after venepuncture. Plasma aliquots were snapfrozen and

stored at -80°C. Plasma fibrinogen was determined by the method of Von Clauss,[25] using the reagents of Dade, by the MLA electra 1000C. PAI-1 antigen was determined with Innotest of Innogenetics, Antwerp, Belgium and carried out according to the manufacture procedure.[26] t-PA was measured with bio-functional immunosorbent assay (BIA) from Biopool, Umea, Sweden. C-reactive protein (CRP) was determined with a home made enzyme immuno assay, using antibodies from Dakopatts, Denmark and CRP standard serum of Behringwerke, Marburg, Germany was used as calibrator. High density lipoprotein (HDL) was measured according to the method of Lopez Virella[27] and triglyceride concentration via GPO-PAP method of Boehringer. Insulin has been measured by radioimmunoassay using a commercially available insulin kit of Pharmacia (Uppsala, Sweden). In addition to the manufacturers protocol, samples, standards and controls are pre-treated with cold PEG 6000 (polyethyleneglycol) in a 1 to 1 ratio in order to eliminate interference from (auto)insulin antibodies or proinsulin. Mean inter-assay coefficient of variation was below 7%. Fasting insulin was determined only in a subgroup (35 men, 28 women).

Data-analysis

Mean baseline concentration of fibrinogen, PAI-1 antigen, t-PA activity, insulin and lipids were calculated for subjects in the intervention and the control group. Baseline associations were investigated with linear regression analysis. In addition, crude and adjusted mean differences in PAI-1 antigen, t-PA activity and fibrinogen between elderly persons active in sport at baseline (light/moderate and strenuous) and non-exercising elderly were calculated, using regression analysis. Adjustment was made for age (5-year categories), alcohol consumption (yes, no) and smoking (smoker, ex smoker, never smoker) using indicator variables. Changes in PAI-1 antigen, t-PA activity, fibrinogen and characteristics of the insulin resistance syndrome over the intervention period were compared between the intervention and control group, using Students t-test. In addition, we stratified the analysis for smoking habits, engagement in sport at baseline and age (60-70 and 70-80 years).

To investigate whether changes in the fibrinolytic factors and fibrinogen coincided with changes in insulin resistance in subjects of intervention and control group, we performed a regression analysis in which change in fibrinolytic factors and fibrinogen were included as dependent variate and intervention assignment and change in features of the insulin resistance syndrome were included as independent variates. Mean baseline CRP, but not mean change in CRP was logtransformed because of its skewed distribution. The statistical package we used was SAS 6.09 (Statistical Analyses System; SAS Institute Inc. Cary, USA).

RESULTS

Baseline data

Table 3.1 presents mean baseline characteristics of men and women in the intervention and control group. Elderly persons of our study had normal mean body mass index and lipid concentrations. No differences were observed between men and women (intervention and control group combined) in mean (± SD) PAI-1 antigen (52.6 ± 29.2 and 52.8 ± 29.0 ng/mL respectively), fibrinogen (3.19 ± 0.70 and 3.19 ± 0.52 g/L respectively) and t-PA activity (0.64 ± 0.33 and 0.64 ± 0.35 IU/mL respectively) (data not shown in table). The study population comprised a rather large proportion of elderly persons who were already engaged in sport activities at the study entry.

Table 3.2 shows the association between PAI-1, t-PA and fibrinogen on the one hand and age, factors of the insulin resistance syndrome on the other. In this elderly population PAI-1 antigen was positively associated with body mass index, diastolic blood pressure, triglycerides, HDL (inversely), fasting glucose and fasting insulin. In men (data not shown), PAI-1 antigen was also inversely associated with physical fitness ($\beta = -1.5$ ng/ml per 10 Watt increase). Although less strongly than PAI-1 antigen, t-PA activity was inversely associated with body mass index and diastolic blood pressure and positively associated with HDL (particularly in women). Fibrinogen was related with HDL, fasting insulin

Table 3.1. *Baseline characteristics of intervention and control group (mean ± sd)*

	INTERVENTION			CONTROL		
	Men $n=36$	Women $n=28$	Total $n=64$	Men $n=37$	Women $n=43$	Total $n=80$
PAI-1 antigen (ng/mL)	50.2 ± 27.4	60.0 ± 31.1	54.5 ± 29.3	55.0 ± 31.1	48.0 ± 26.8	51.3 ± 28.9
t-PA activity (IU/mL)	0.67 ± 0.35	0.58 ± 0.32	0.63 ± 0.34	0.62 ± 0.31	0.68 ± 0.37	0.66 ± 0.34
Fibrinogen (g/L)	3.12 ± 0.63	3.23 ± 0.43	3.17 ± 0.55	3.26 ± 0.77	3.16 ± 0.58	3.21 ± 0.67
C-reactive protein (mg/L)[‡]	1.36 ± 2.81	1.38 ± 2.61	1.37 ± 2.70	1.51 ± 2.94	1.02 ± 3.06	1.21 ± 3.04
Insulin (mU/L)[†]	9.02 ± 3.41	7.65 ± 2.39	8.50 ± 3.09	8.46 ± 3.68	8.97 ± 3.80	8.73 ± 3.69
Body mass index (kg/m^2)	24.9 ± 2.4	25.6 ± 3.0	25.2 ± 2.7	25.3 ± 3.0	24.3 ± 3.8	24.7 ± 3.5
HDL (mmol/L)	1.07 ± 0.25	1.15 ± 0.24	1.10 ± 0.25	1.09 ± 0.27	1.26 ± 0.31	1.18 ± 0.30
Triglycerides (mmol/L)[#]	1.44 ± 0.69	1.49 ± 0.57	1.46 ± 0.64	1.53 ± 1.06	1.31 ± 0.50	1.41 ± 0.81
Age (years)	68.3 ± 5.2	68.1 ± 5.5	68.2 ± 5.3	68.9 ± 5.6	69.0 ± 5.2	68.9 ± 5.4
Maximal Work rate (Watt)	168.6 ± 35.1	124.3 ± 36.1	149.2 ± 41.6	152.6 ± 41.8	113.0 ± 28.2	130.8 ± 39.9
Smokers (%)	25.0	14.3	20.3	29.7	14.0	21.3
Alcohol drinkers (%)	83.3	42.9	65.6	89.2	51.2	68.8
Active in sport (%)	41.7	50.0	45.3	29.7	44.2	37.5

[†] geometric mean [‡] subjects with insulin concentration > 20 mU/l excluded (n = 3), [#] non fasting subjects excluded (n = 2).

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and physical fitness (Wmax). Only in women (data not in table), fibrinogen was significantly associated with triglycerides ($\beta = 0.34$ g/l per 1 mmol/L increase) and body mass index ($\beta = 0.04$ g/l per 1 kg/m^2 increase). The association of fasting insulin with PAI-1 antigen was independent of triglyceride and HDL level, body mass index and diastolic blood pressure in women ($\beta = 2.28$, $P < 0.05$) but not in men ($\beta = 0.99$, $P = 0.47$). Three subjects had extreme high fasting insulin (outliers) and were excluded from the insulin analyses, since they modified the results to a great extent.

Table 3.2. *Association[†] between baseline PAI-1 antigen, t-PA activity and fibrinogen and characteristics of the insulin resistance syndrome.*

	PAI1-ag	t-PA activity	Fibrinogen
	β	β	β
Age	0.2	0.01	0.01
Body mass index (kg/m^2)	5.1***	-0.05***	0.01
Diastolic BP (mmHg)	0.6*	-0.01*	-0.00
Triglycerides[#](mmol/L)	11.6***	-0.02	-0.00
HDL (mmol/L)	-28.4**	0.22*	-0.38*
Insulin[‡](mU/L)	2.5**	-0.01	0.05*
Maximal work rate (10 Watt)	-0.9	-0.01	-0.03*

[†] regression coefficients, adjusted for sex
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$
[#] non fasting subjects excluded, (n = 2)
[‡] subjects with insulin > 20 mU/L excluded (n = 3).

Table 3.3 shows crude and multivariate adjusted mean difference in PAI-1, t-PA and fibrinogen between subjects active in sport at baseline (moderate/light or strenuous activity) and those who were not. Among the subjects, 28.5% (n = 41) performed (mainly) strenuous activity (mean ± sd: 8.1 ± 8.2 hrs/month) and 12.5% (n = 18) performed (mainly) moderate and light activity

(20.7 ± 16.3 hrs/month). Strenuous activity included gymnastics, swimming and exercise biking, jogging and tennis (single). Moderate and light activity included yoga, tennis (double), brisk walking, golf and horseback riding. Subjects who performed moderate and light activity had lower PAI-1 antigen, fibrinogen and t-PA activity. Subjects who performed strenuous exercise had higher PAI-1 levels and lower t-PA activity. Except for the crude difference in fibrinogen, none of these differences were statistically significant.

Table 3.3. *Crude and adjusted baseline differences (mean ± SE) of PAI-1 antigen, t-PA activity and fibrinogen between elderly persons active in sport as compared to elderly persons not active in sport (n = 85).*

Active in sport:	Moderate/light [†] n = 18	Strenuous [‡] n = 41
PAI1-ag (ng/mL)		
crude	-5.7 ± 7.5	4.1 ± 5.6
multivariate adjusted[§]	-5.7 ± 7.8	4.3 ± 6.0
t-PA activity (IU/mL)		
crude	-0.12 ± 0.09	-0.09 ± 0.07
multivariate adjusted	-0.11 ± 0.09	-0.07 ± 0.07
Fibrinogen (g/L)		
crude	-0.27 ± 0.16*	-0.03 ± 0.12
multivariate adjusted	-0.17 ± 0.16	0.04 ± 0.12

* $0.1 < P < 0.05$
[†] Moderate/light activity: yoga, tennis-double, golf, horse riding, volleyball, table tennis (intervention n = 10, control n = 8).
[‡] Strenuous activity: gymnastics, jogging, exercise biking, swimming, tennis-single (intervention n = 19, control n = 21).
[§] multivariate adjustment: sex, age (5 year category), smoking (yes, ex smoker, never smoker) and alcohol consumption (yes/no)

Table 3.4. Mean change (± SE) after 6 months follow up in fibrinolytic factors, fibrinogen, C-reactive protein and components of the insulin resistance syndrome in elderly subjects of intervention and control group

change in:	INTERVENTION			CONTROL		
	Men n=36	Women n=28	Total n=64	Men n=37	Women n=43	Total n=80
t-PA activity (IU/mL)	0.09 ± 0.05*	0.05 ± 0.06	0.07 ± 0.04*	-0.04 ± 0.04	-0.02 ± 0.04	-0.03 ± 0.03
PAI1-ag (ng/mL)	-1.57 ± 3.00	-2.66 ± 3.97	-2.05 ± 2.40	-0.78 ± 4.35	3.76 ± 3.38	1.63 ± 2.71
Fibrinogen (g/L)	0.18 ± 0.10*	0.17 ± 0.09	0.18 ± 0.07**	-0.26 ± 0.11	0.08 ± 0.06	-0.07 ± 0.06
C-reactive protein (mg/L)	0.54 ± 0.67	0.84 ± 1.20	0.67 ± 0.64	-0.84 ± 0.76	-0.01 ± 0.43	-0.38 ± 0.41
Insulin (mU/L)	0.11 ± 0.54	0.39 ± 0.30	0.22 ± 0.36	-0.31 ± 0.39	0.62 ± 0.69	0.11 ± 0.38
Weight (kg)	-0.10 ± 0.32	-0.28 ± 0.39	-0.18 ± 0.25	-0.03 ± 0.38	-0.17 ± 0.27	-0.11 ± 0.22
HDL (mmol/L)	0.16 ± 0.03	0.18 ± 0.05	0.17 ± 0.03	0.08 ± 0.04	0.12 ± 0.04	0.10 ± 0.03
Triglycerides (mmol/L)	-0.05 ± 0.08	-0.18 ± 0.08*	-0.11 ± 0.06	-0.01 ± 0.13	0.05 ± 0.05	-0.02 ± 0.07
Diastolic BP (mmHg)	-6.9 ± 1.2	-4.5 ± 1.6	-5.9 ± 1.0	-3.5 ± 1.5	-5.0 ± 1.2	-4.3 ± 0.9
Maximal capacity (Watt)	20.3 ± 4.1***	10.4 ± 3.2***	15.9 ± 2.7***	4.4 ± 3.1	-6.6 ± 3.3	-1.4 ± 2.3

* P < 0.05, ** P < 0.01, *** P < 0.001 Students T-test difference in change between intervention and control

Changes during intervention

Table 3.4 shows the mean change in the acute phase proteins, physical fitness and some characteristics of the insulin resistance syndrome for men and women in intervention and control group. Subjects of the intervention group significantly increased their physical fitness, men with 12% and women with 8%. Also, t-PA activity was significantly increased among subjects of the intervention group compared to the change in the control group. Mean PAI-1 antigen was modestly decreased in the subjects of the intervention group. The greatest decrease was observed in women who were inactive before the intervention (13%, -7.6 ± 5.9 ng/mL). Mean change in PAI-1 antigen was however not significantly different from the changes in the controls.

Unexpectedly, fibrinogen was significantly increased in subjects of the intervention group as compared to the controls, notably among men aged 70 to 80 (mean 0.25 ± SE 0.25 mg/L) and women, who were previously not active in sport (mean 0.34 ± SE 0.14 mg/L). Note, however, that increase in intervention men was smaller than the fall in the controls. Effects of training were not different among smokers as compared to non smokers (data not shown).

Table 3.5 shows the crude and multivariate adjusted mean difference in PAI-1 antigen, t-PA activity and fibrinogen between the intervention and control group (β of intervention). The multivariate adjusted regression coefficients of intervention are attenuated for PAI-1 antigen as compared to the crude coefficients, indicating a possible mediating role of the adjusting factors in the training response. Change in triglycerides was significantly associated with change in PAI-1 antigen ($P < 0.01$). Increase in fibrinogen was significantly associated with a decrease in HDL. The latter association attenuated after inclusion of change in C-reactive protein (a marker of inflammation and a possible marker for atherosclerosis) in the model, which itself was highly correlated with fibrinogen change. Adjustment did not affect the observed difference in change of t-PA activity in intervention and control group.

In a subpopulation (n = 63), of persons for whom serum insulin concentration was available, a regression model including insulin showed that change in insulin was associated with change in PAI-1 antigen (β = 2.37 ng/ml per 1 mU/L, P = 0.07) and change in fibrinogen (β = 0.09 g/l per 1 mU/L, P = 0.03). Change in saturated fat or total fat intake, administered by a food frequency questionnaire[27] did not have any association with change in PAI-1 antigen or fibrinogen.

All analyses were also performed with exclusion of non fasting subjects and one subject who started new medication during the intervention, but this did not alter the results.

Table 3.5. *Association between 6-months change in PAI-1 antigen (ng/mL), t-PA activity (IU/mL) and fibrinogen (g/L) with change in risk factors involved in the insulin resistance syndrome, univariate and multivariate regression models.*

change in:	PAI-1 ag	t-PA activity	Fibrinogen	
Univariate				
intercept	1.68	-0.03	-0.08	
intervention[†]	-3.73	0.10*	0.26**	
Multivariate			model 1	model 2
intercept	4.33	-0.04	0.05	0.04
intervention	-1.72	0.10	0.31***	0.28**
sex[‡]	-3.74	0.02	-0.20*	-0.20*
change in weight (kg)	1.11	0.00	0.02	0.02
change in HDL (mmol/L)	-6.36	0.13	-0.51*	-0.28
change in triglycerides (mmol/L)	10.45**	0.07	-0.08	0.00
change in diastolic BP (mmHg)	-0.05	0.00	-0.01	0.00
change in CRP (mg/L)				0.05***

* P < 0.05, ** P < 0.01, *** P < 0.001

[†] 1 = intervention 0 = control

[‡] 1 = men 0 = women

DISCUSSION

Several studies have identified increased fibrinogen and PAI-1 as predictors of coronary heart disease in healthy subjects[1,29,30] and patients.[31,32] Both factors attribute to risk similar to serum total cholesterol. In a controlled intervention study among elderly people we observed that a 6 months training programme resulted in a moderately increased fibrinolytic activity (decrease in PAI-1 antigen and increase in t-PA activity) in both men and women of the intervention group. Reduction in PAI-1 was significantly associated with a decrease in triglycerides. Unexpectedly, fibrinogen was significantly increased in elderly subjects following the exercise programme, especially in women not previously engaged in sports. Increase in fibrinogen was significantly associated with a rise in C-reactive protein, which suggests a contribution of an acute phase response. The cross sectional analysis showed a lower fibrinogen level in subjects active in moderate sport at baseline, but correction for age, smoking and alcohol consumption attenuated the difference.

The selective nature of our study population (41% was active in sport at baseline) limits generalizability of the results. It is, however, neither feasible nor ethical to conduct a 6 months intervention study among less fit elderly subjects, who are more prone to risk of coronary heart disease and sport injuries. Also in our study less fit elderly had more problems with adherence to the programme and were more prone to drop out. Unfortunately, we do not have information on fibrinogen or fibrinolytic factors in subjects who dropped out of the study and we do not know whether this selective drop out may have confounded the association. Since greater effects are expected in less fit elderly, we assume that this selective drop out may have caused an underestimation of the effect.

Fibrinogen

Until now cross-sectional studies gave strong indication for an inverse relationship between exercise and fibrinogen and also in patients beneficial

effects of training were observed.[33] However, most training studies in healthy persons failed to observe a significant training effect on fibrinogen,[19,21] except for Stratton *et al.,*[18] who did find a reduction in fibrinogen in elderly men undertaking strenuous exercise. These men, however had extremely high fibrinogen levels (3.57 ± 0.79 g /L) and regression to the mean could have played a role. In our study, the observed increase in fibrinogen was apparent in most subjects of the intervention group and not caused by a few outliers.

Although unexpected, our results are not completely opposite to previously reported studies. Ponjee *et al.*[22] also observed a significant increase in fibrinogen of 0.78 g/L in middle aged subjects preparing for running half a marathon. Recently, Montgomery *et al.*[34] reported an increase in fibrinogen, in men two days after a very strenuous training programme, which gradually declined after four days. This increase was thought to be due to an 'acute phase response' to the strenuous exercise. Earlier Weight *et al.*[35] reported increases in fibrinogen and CRP, 48 hours after extreme exercise in competitive distance runners. Although the activity level in our group was not as strenuous as mentioned in the study of Montgomery, it is possible that less intensive bouts of exercise already lead to elevated acute phase protein levels in elderly persons. The longer recovering process in elderly as compared to middle aged and young subjects, may prolong the acute phase response and consequently may lead to chronically elevated acute phase protein levels when they exercise intensively on a regular base. (Note that subjects with arthritis did not have higher baseline concentration of CRP or fibrinogen, nor did they have a larger increase in these proteins after exercise intervention). The study of Rankinen *et al.,*[14] in which subjects who exercised 6 times a week for 6 months had an increase in fibrinogen, while those who exercised less had a decrease in fibrinogen (not significant), is in line with this hypothesis. Also our baseline data suggest more favourable effects of moderate exercise than strenuous exercise. Moderate activity was, however, performed more frequently and over a longer period of time than strenuous exercise. In contrast with our baseline results, Connelly *et al.*[36] reported significantly lower fibrinogen levels in subjects performing strenuous exercise than mild exercise.

Another possible explanation for the observed elevated levels of fibrinogen and CRP in our study (although less likely) may be that these are a

consequence of regression of atherosclerosis induced by training. The repair process, during atherosclerotic regression, may be accompanied by increases in pro-inflammatory proteins, such as fibrinogen and CRP. Reason for not observing significant changes in CRP in the intervention group may be due to the short half life of CRP (6 hrs) as compared to fibrinogen (2.5 days). Finally, next to physical stress, the exercise programme could also have caused psychological stress, which is also related to increased levels of fibrinogen.[37,38] Clearly, more research is needed to clarify effects of training on fibrinogen. Present knowledge does not provide sufficient proof that elderly persons should avoid high intensity activity.

PAI-1 antigen and t-PA activity

Subjects in our intervention group had an increased fibrinolytic potential after 6 months training, due to a beneficial shift in PAI-1 and t-PA, which may be a result of a reduced formation of t-PA/PAI-1 complexes. Our results are in line with earlier described studies, although less convincing. Ponjee *et al.*[22] found a 75% reduction in PAI-1 antigen in 34 sedentary men and women who had been training for 36 weeks. Stratton *et al.*[18] observed a reduction in PAI-activity (58%) and increase in t-PA activity (141%) in 13 elderly men following a 6 months intensive training programme.

Contrary to participants in these studies, our group of elderly was not completely sedentary at baseline. In fact, 41% of our population was already engaged in sport activities. When we included solely sedentary subjects in our analysis, greater training effects were observed, especially in women. Still, some other training studies did not find any effect on fibrinolytic activity. In the mentioned study of Stratton, an intensive training programme did not affect fibrinolysis in young males. Also De Geus *et al.*[20], Rankinen *et al.*[19] and Anderssen *et al.*[21] did not observe significant changes in fibrinolytic factors in response to a training programme. Yet, the intensity and frequency of the training programmes of these studies was similar to our study (De Geus: 2.5 hours per week 70% of maximal exercise capacity, Rankinen: 2 to 6 times a

week on an intensity of 55 to 65% of VO_2max, Anderssen: 3 times a week 60-80% of peak heart rate). The different study designs and populations make comparisons difficult and so far no conclusive statement can be made on the relationship between physical activity and fibrinolysis.

Relationship between fibrinogen, PAI-1 antigen and insulin resistance

In this study we were interested in the question whether changes in fibrinogen and fibrinolytic activity induced by training were accompanied by changes in features of the insulin resistance syndrome. Various studies have reported an association between PAI-1 and fibrinogen with triglycerides, HDL and diastolic blood pressure, but failed to show an independent association with insulin sensitivity or glucose tolerance.[39,40] Our study confirmed the association between the acute phase proteins and body mass index, triglycerides, HDL and diastolic blood pressure in an elderly population, but the associations were stronger in women than in men. This might be explained by 1) greater inter person variation of insulin resistance in women, leading to increased statistical discrimination 2) a possible higher prevalence of insulin resistance in women.

Decrease in PAI-1, was accompanied by a reduction in triglycerides (significant), body mass and insulin and an increase with HDL, indicating a possible mediating role of insulin resistance in the association between physical activity and PAI-1. Until now only a few other studies have looked into the interrelationship between the changes in these properties.[20,22,41] Ponjee *et al* [22] and the Geus *et al.*[20] do not find a relationship between training induced changes in PAI-1 and maximal oxygen consumption, diastolic blood pressure, lipids and body fat. Boman *et al.*,[41] on the other hand, observed a significant reduction in PAI-1 in subjects doing a 14-day skiing tour, which appeared to be mediated through change in body fat mass and increased insulin sensitivity.

In summary, the present data suggest beneficial effects of physical training on fibrinolysis. Fibrinogen and CRP were, however, elevated in subjects following the intervention programme. It is unclear whether this represents a favourable or an unfavourable effect. Since increase in fibrinogen coincided with an

increase in fibrinolytic activity, there is not sufficient reason to expect higher coagulability in these elderly. Possibly a shift in the balance between coagulation and fibrinolysis has occurred. This shift may provide a quicker response to vessel damage, without higher risk of thrombus formation. Since increase in fibrinogen seems to occur particularly after strenuous exercise, at present the only safe recommendation for elderly people seems to be to perform moderate exercise on a regular basis.

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CHAPTER 4

Physical training reduces QT_c interval among elderly people

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ABSTRACT

Prolongation of heart rate adjusted QT-duration (QT_c) is associated with an increased risk of coronary heart disease mortality. QT_c is influenced by autonomic cardiac control. Since previous studies have shown improvement of autonomic balance by physical activity, QT_c might reduce when people become more active.

In a controlled intervention study among 229 healthy elderly subjects (aged 60-80 years), the effect of regular intensive physical activity on QT_c was studied. Subjects of the intervention group trained 3 to 4 times a week, during 6 months. Mean QT_c-duration (ms) in women of the intervention group changed -6.7 ± 2.8 (SE), versus 0.6 ± 2.4 (SE) in the control group ($P=0.05$), while in men of the intervention group the change was -2.7 ± 2.2 versus 0.4 ± 3.1 in the control men ($P=0.39$). Also resting heart rate (beats/min) changed in intervention women with -4.6 ± 1.7 as compared to -0.06 ± 1.1 in the controls ($P=0.02$) and in intervention men with -3.2 ± 1.2 versus -0.9 ± 1.5 in the controls ($P=0.25$).

These data indicate that regular physical activity favourably affects QT_c in elderly persons. Changes were most pronounced in women. The beneficial shift in QT_c may be caused by a more favourable autonomic balance through increased parasympathetic activity. The reduced resting heart rate in subjects of the intervention group is in agreement with this.

INTRODUCTION

A prolonged heart rate adjusted QT-duration (QT$_C$) was found to be a risk factor for sudden death in myocardial infarction patients[1-3] and in patients who had diagnostic 24-hour electrocardiography.[4] There is increasing evidence that a prolonged QT$_C$ is predictive for coronary heart disease mortality in healthy populations as well.[5,6] QT$_C$ prolongation may be a consequence of an unfavourable balance between sympathetic and parasympathetic activity. Sympathetic predominance accompanied by dispersion of repolarisation reflected in QT prolongation may cause ventricular electrical instability and increase risk of fatal myocardial infarction.[7,8]

It has been speculated that change in autonomic balance contributes to the age-related prolongation of QT$_C$. In this context a preventive role of physical activity was hypothesized.[6] Regular physical activity seems to improve cardiac electrical stability and autonomic control.[9,10] It stimulates parasympathetic activity and hereby favours the balance between sympathetic and parasympathetic activity.[10]

Unpublished results of a cross sectional study, performed by our group, among elderly (65 to 85 years of age), indeed indicated a significant inverse association between habitual physical activity and QT$_C$. However, the design of that study precluded conclusions on the causality of the association. We therefore investigated the relation between physical activity and QT$_C$-duration in a trial. In addition we looked at training effects on resting heart rate, since changes in heart rate probably also reflect changes in parasympathetic tone. In our study, changes in QT$_C$ and heart rate were compared between subjects following a 6 months intensive training programme and control subjects, who retained their habitual activity.

SUBJECTS AND METHODS

Study population

The study population comprised caucasian elderly people, aged between 60 and 80 years and living in Arnhem, the Netherlands. 829 Elderly persons, recruited from a general practice, were invited to participate in an intervention study investigating the effect of training on coronary risk factors. These apparently healthy persons were without angina pectoris, heart failure, hypertension (diastolic pressure > 115 mm Hg), insulin-dependent diabetes mellitus and did not use beta-blockers. None of these elderly had a myocardial infarction or a stroke in the past 2 years. From these, 318 elderly were willing to participate. Reasons for non-participation were mainly no time (46.6%) or no interest (24.6%). Participating elderly were relatively active: 77% of the participants considered themselves more active than their peers, versus 49% of the refusers.

To make sure subjects were fit to participate in a physical exercise programme, a medical examination was performed, including resting and exercise electrocardiography and a blood pressure measurement. The results were reviewed by a general practitioner and a cardiologist. In total 39 men and 50 women were excluded from participation, of whom 29 women and 30 men because of abnormalities in resting or exercise electrocardiogram.

The remaining 229 subjects (113 men and 116 women) were distributed at random to one of three protocols; an exercise bicycle group (48 men and 48 women), an all-round activity group (25 men and 22 women) and a control group (40 men and 46 women). Husbands and wives were randomised together.

During the intervention 18 men and 24 women prematurely left one of the training programmes while 2 men and 2 women dropped out of the control group. In the intervention group drop out was mainly caused by motivation problems (50%) and medical reasons (40%). In the control group drop out was mainly caused by family circumstances. Because of missing values in pre-intervention QT_c measurement, 5 men and 3 women were excluded from all analyses. Subjects with a missing on post intervention QT_c measurement (2

men and 1 woman of the intervention group) were excluded from the prospective analyses only.

Training Protocols

The elderly allocated to the exercise bicycle group received an exercise bike at home on which they exercised four times a week, for 30 minutes, during half a year. In the first 5 weeks the level was gradually increased to a heart rate corresponding to 70% of their maximal exercise capacity (Wmax), which was individually determined in an exercise bicycle test at baseline.

Subjects in the all-round activity group exercised 3 times a week for 45 minutes during half a year. The training was given by an experienced sports instructor and comprised aerobic exercise, callisthenics, and flexibility exercises. In the present study, elderly of the two intervention groups were combined, since both training protocols were similar with respect to intensity and duration. Elderly of the control group were asked to retain their habitual activities during the intervention period.

Adherence to the programme was stimulated by regular telephone calls (3 times in 6 months), a personal visit and some social happenings. Adherence in the bicycle group was checked with a cycling record. Men and women of the bicycle group who completed the programme, on average performed 86% and 81% respectively of the prescribed training, while in the all-round activity group men and women on average performed 72% and 81% of the training respectively. The protocol for the intervention was approved by the Medical Ethical Committee of the Wageningen Agricultural University and was fully explained to the subjects. All subjects gave their written informed consent.

Data collection
All subjects underwent an examination at the beginning and end of the intervention period, which comprised electrocardiography, anthropometry, blood pressure measurements, blood sampling and an exercise tolerance test.

Weight and height were measured (wearing underclothes, without shoes) and used to calculate the Body Mass Index (kg/m^2). Blood pressure was measured three times after a resting period of 30 minutes, while subjects were sitting. Mean values of the last two measurements were used in the analysis. Maximal exercise testing was performed on a bicycle ergometer. Initial ergometer workload, 30 Watt for women and 60 Watt for men, was increased by 30 Watt every 3 minutes. This protocol was used in order to approach a steady state at each level and to perform cardiovascular screening simultaneously. The test was stopped when the subjects were exhausted or when there was a medical indication for premature halt. Maximal exercise capacity (Wmax) was determined through interpolation by summing up 10 Watt for every extra full minute of cycling on a certain work load.

Standard resting 12-lead electrocardiograms were made using a Marquette electrocardiographic recorder. QT-intervals were measured using a digitising tablet (Calcomp) and a personal computer. The resolution of this tablet is 100 lines/mm and the reproducibility is 0.25 mm (corresponding to 10 msec). QT-intervals were read from three leads: V2, V6 and of I, II or III the lead with the longest QT. In each lead, QT-intervals and the preceding RR-intervals were measured in three consecutive normal complexes. The beginning of the QT-interval was defined as the first deflection of the QRS complex, the end as the point of maximal change in the slope as the T-wave merges with the baseline.[11] One person measured all the intervals, blinded for intervention or control status. QT-intervals were adjusted for heart rate according to Bazett's method.[12] Means of 3 heart-rate adjusted QT-intervals from each lead were calculated. The longest mean QT$_c$-interval was used for the analysis.

Venous blood samples were taken after an overnight fast. High density lipoprotein (HDL) cholesterol was measured in serum supernatant with the enzymatic "CHOD-PAP-Monotest"-method of Boehringer.[13] Total triglycerides content was determined in serum by the enzymatic "GPO-PAP"-method of Boehringer.[14] Insulin has been measured by radioimmunoassay using a commercially available insulin kit of Pharmacia, Uppsala, Sweden.

Habitual physical activity was assessed with the questionnaire previously described by Caspersen *et al.*[15] Medical history, socio-demographic

characteristics and information on smoking habits and use of medication were assessed in a personal interview.

Data analysis

Because women in general have longer QT$_C$ than men, analyses were performed separately. Mean values of baseline characteristics were calculated for men and women and compared between elderly of the intervention group (bicycle and all round group combined) and control group. In addition, mean QT$_C$ intervals were compared for subjects active in sport and subjects refraining from sport; crude means with Students t-test and age adjusted means with an analysis of covariance (least square means). The effect of the training programme was investigated by comparing changes in QT$_C$ interval and resting heart rate between subjects of the intervention group and control group, using Students t-test. Data were analysed using SAS software.[16]

RESULTS

Table 4.1 shows the baseline characteristics of the study population of men and women of the intervention and control group, who stayed in the study until the end. The intervention and control group differed with respect to age (women), sport activity (men) and physical fitness (men). Other characteristics were not different between intervention and control group. Mean QT$_C$ was **418** ms in men and **427** ms in women. Mean (unadjusted) QT was **389** ms in both sexes.

Table 4.2 shows mean QT$_C$, resting heart rate, age and fitness of elderly in categories of sport engagement. Mean QT$_C$ of elderly men who (mainly) exercised strenuously at baseline was somewhat lower than men who did not exercise at all. Women, but not men, who performed (mainly) light and moderate sport, also had a lower mean QT$_C$ interval, but this group was rather

small. In general, exercising subjects were younger and physically more fit than those who did not exercise. Crude and age- adjusted differences in QT_C were not significant between the groups. In line with this, time spent on sport activity (min/week) and maximal exercise capacity (Watt) were not significantly associated with the length of QT_C, using age-adjusted regression analysis

Table 4.1. *Baseline Characteristics of study population (mean ± sd)*

| | INTERVENTION | | CONTROL | |
	Men (n = 53)	Women (n = 44)	Men (n = 34)	Women (n = 43)
Age (years)	67.3 ± 4.9	66.7 ± 5.4	69.2 ± 5.6	69.1 ± 5.2
Body Mass Index (kg/m²)	25.2 ± 2.6	25.7 ± 3.5	25.0 ± 2.9	24.2 ± 3.8
QTc (ms)	417.8 ± 22.9	425.8 ± 20.3	417.5 ± 23.2	427.4 ± 18.4
QT (ms)	386.0 ± 27.2	383.5 ± 23.9	394.7 ± 21.4	395.3 ± 24.2
Resting Heart rate (b/m)	70.9 ± 12.5	74.4 ± 11.3	67.1 ± 9.9	70.2 ± 8.2
Diastolic BP (mmHg)	82.5 ± 9.6	82.6 ± 10.1	85.6 ± 11.1	86.1 ± 10.1
HDL (mmol/L)	1.12 ± 0.26	1.22 ± 0.29	1.07 ± 0.28	1.27 ± 0.33
Triglycerides (mmol/L)	1.46 ± 0.87	1.47 ± 0.55	1.58 ± 1.09	1.31 ± 0.50
Maximal work rate (Watt)	179.6 ± 41.0	125.7 ± 32.9	151.8 ± 42.1	113.0 ± 28.2
Active in sport (%)	50.9	54.6	26.5	44.2
Smoking (%)	26.4	13.6	26.5	10.0

In **Table 4.3.** and **Figure 1** the effect of the training intervention on QT_C and resting heart rate is shown. In both men and women of the intervention group, a reduction in QT_C duration and resting heart rate was observed, but only in women the association was significant. When the analysis were restricted to subjects who were not active in sport at baseline, results slightly changed for men (intervention: -1.4 ± 2.6 ms, control: 1.1 ± 3.0 ms) but in women effect of training became even more pronounced (intervention: -9.7 ± 5.0 ms, control: 3.8 ± 2.8 ms, $P = 0.02$).

Table 4.2. *Mean (± sd) QT$_C$ interval, resting heart rate, age and fitness of men and women in categories of sport engagement at baseline.*

Sport activity	no	light/moderate	strenuous
Men	*(n = 51)*	*(n = 12)*	*(n = 24)*
QT$_C$ (ms)	418.7 ± 22.3	418.7 ± 30.1	415.0 ± 20.8
Resting heart rate (b/m)	70.1 ± 10.1	65.0 ± 12.5	70.2 ± 14.2
Age (years)	69.4 ± 5.4	67.6 ± 5.8	65.4 ± 3.6
Maximal work rate (Watt)	157.0 ± 37.9	175.8 ± 43.6	190.4 ± 46.4
sport hours/month	0	25.0 ± 17.5	9.2 ± 6.4
Women	*(n = 44)*	*(n = 6)*	*(n = 37)*
QT$_C$ (ms)	428.7 ± 21.3	422.7 ± 15.3	424.7 ± 17.5
Resting heart rate (b/m)	73.5 ± 11.7	69.6 ± 7.9	71.3 ± 8.1
Age (years)	68.7 ± 5.4	68.7 ± 7.0	66.8 ± 5.1
Maximal work rate (Watt)	108.6 ± 30.2	125.0 ± 44.6	131.4 ± 25.7
sport hours/month	0	12.5 ± 9.7	8.0 ± 8.3

Light/moderate activity: yoga, golf, tennis double, volleyball, table tennis, horse riding
strenuous activity: gymnastics, jogging, exercise biking, swimming, tennis single

Table 4.3. *Change in heart rate and QT$_C$ interval (mean ± SE) during the intervention period in men and women*

	INTERVENTION		CONTROL	
	Men	**Women**	**Men**	**Women**
	(n = 53)	*(n = 44)*	*(n = 34)*	*(n = 43)*
change in:				
QT$_C$ interval‡ (ms)	-2.7 ± 2.2	-6.7 ± 2.8*	0.4 ± 3.1	0.6 ± 2.4
Heart rate (b/min)	-3.2 ± 1.2	-4.6 ± 1.6*	-0.9 ± 1.5	-0.1 ± 1.1
Maximal capacity (Watt)	16.0 ± 3.2*	11.7 ± 2.6†	3.6 ± 3.2	-6.5 ± 3.4

* *P* <0.05, † *P* < 0.001, Students t-test: intervention vs control group:
‡ longest QT$_C$ interval

Figure 4.1. *Mean pre- and post intervention QT_C interval (ms) among elderly of the exercise and control group.*

| pre intervention | post intervention |

mean QTc interval (ms)

* p < 0.05   MEN   WOMEN
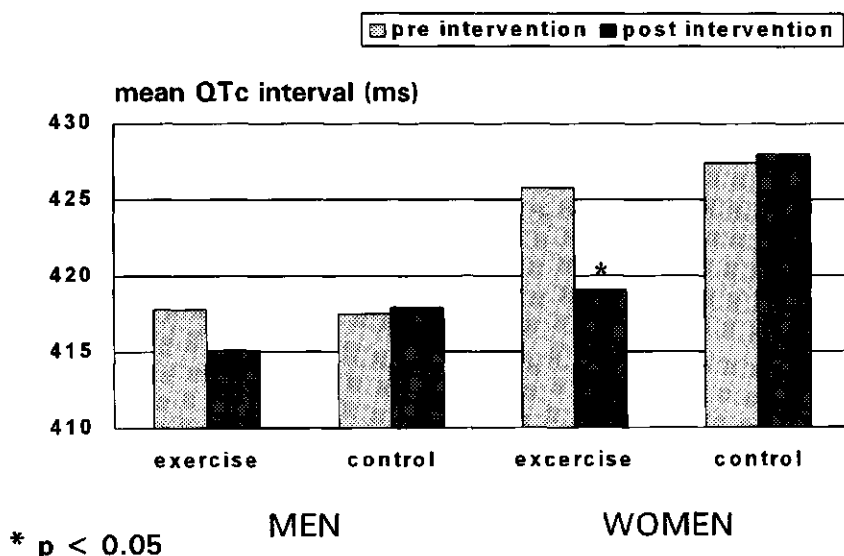
DISCUSSION

In this intervention study we observed a reduction in QT_C and resting heart rate in men and women participating in a 6 months training programme as compared to a control group. The reduction in QT_C and heart rate was however, more pronounced, and only significant in women. The difference between men and women was mainly a result of a strong training effect in women who were inactive at baseline and therefore probably more susceptible for training effects. Our cross sectional data were less convincing. Although men and women active in sport at baseline had lower QT_C intervals, this was not significantly different from elderly inactive in sport. Until now, there are no published data on the association between physical activity and QT_C duration and also possible effects of physical training on QT_C in elderly have not been reported before.

The results of our study may therefore add some new information on the beneficial impact of exercise on cardiovascular risk.

It has been postulated that QT$_C$ is prolonged among subjects with an unfavourable balance between sympathetic and parasympathetic activity. Previous studies using pharmacological interventions confirmed effects of change of parasympathetic tone on QT$_C$ interval. Anilla *et al.*[17] have described QT$_C$ prolongation as a result of administering atropine, a parasympathetic blocking agent. After adrenergic blockade the QT-interval was shortened again. Therefore, we suggest that the observed reduction in QT$_C$ in men and women of our training group may result from an increase in parasympathetic activity. Also, the observed decrease in resting heart rate and the strong correlation between change in QT$_C$ and change in mean resting heart rate (r = 0.47, P < 0.001), may suggest that both changes have a similar background, namely a change in cardiac autonomic control. Our results are in line with earlier studies which have shown that people active in sport have (cross-sectional studies) or obtain (longitudinal studies) higher parasympathetic activity and a better balance between sympathetic and parasympathetic activity.[10,18] Also training studies in dogs[9,19] have shown a shift in autonomic balance characterised by increased cardiac vagal activity, accompanied by lower risk of ventricular fibrillation.

The observed reduction in QT$_C$ may also have resulted from changes in characteristics of the insulin resistance syndrome. Previous observations suggest excessive activation of the sympathetic nervous system in subjects with the insulin resistance syndrome[20]. A reduction in body fat, induced by training, may cause a reduction in free fatty acids and consequently result in lower plasma insulin levels. This may then further indirectly lead to a reduction in sympathetic activity. Baseline data indeed showed a cross sectional association between QT$_C$ and some features of the insulin resistance syndrome; body mass index (r = 0.20, P = 0.01), triglyceride concentration (r = 0.16, P = 0.04), HDL (r = -0.17, P = 0.03) and fasting insulin (r = 0.17, P = 0.09) in subjects of our study. However, we did not observe any significant association between change in these parameters during the intervention with change in QT$_C$

(change in weight $r = 0.11$, $P = 0.14$, triglycerides $r = 0.01$, $P = 0.89$, or fasting insulin $r = -0.03$, $P = 0.77$), providing no indication that change in QT_C might be a consequence of change in insulin resistance.

The study results might have been subject to some potential errors. Misclassification in measurement and coding of the QT-interval may have occurred. To assure the closest approximation to the maximum QT interval, we measured QT-intervals in 3 leads (I, II or III, V2 and V6) in which axes are nearly orthogonal, and selected the longest QT interval. QT-intervals were measured by one person, blinded with respect to the status of a subject, to avoid bias due to interobserver differences and differential error. The measured QT-interval was adjusted for heart rate according to the Bazett formula[12], which has the purpose of standardising the QT-interval to a heart rate of 60 beats per minute. Although questioned, this correction formula is generally used. Moreover, Bazetts' correction functions fairly well in the heart rate range of 55 to 85 beats/min[21], which applied for 90 % of the men and 87 % of the women of our study.

A bias in the results, because of pharmacological intervention influencing QT_C is not very likely. Subjects who were using beta-blockers were excluded from the study and other medications which can influence the heart or the central nervous system were well-balanced among the intervention and the control group. This medication was not altered during the intervention period.

Our study population consisted of a large group of elderly, who were relatively active and healthy as compared to the general Dutch population. Not only were these elderly subjects screened, those participants who were physically or mentally unable to continue with the intervention programme prematurely left the study. Since drop out during intervention was more frequent in the intervention group, it could have biased the results. However, in general, subjects who dropped out were less physically fit and less active at baseline than the elderly who completed the protocols (compare baseline activity and fitness). Since greater effects are expected in less fit elderly, selection might probably have led to an underestimation of the effect.

In conclusion, elderly subjects who followed a six months training programme showed a decline in QT_C-duration and heart rate as compared to a control group. The reduction in QT_C and heart rate probably reflects an improvement in parasympathetic activity. However, whether the extent of the QT_C change, observed in our study would lead to a reduction in coronary heart disease risk cannot be decided from these results. From our earlier studies on the prognostic values of QT_C for coronary heart disease death, such a protective effect might be inferred.

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CHAPTER 5

Increased heart rate variability by exercise training in elderly men and women

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ABSTRACT

Heart rate variability (HRV), a characteristic that is potentially increased by physical activity, was recently reported to be inversely associated with incidence of cardiac events and total mortality in a community-based population. Since the incidence of cardiac events among elderly is high and their physical activity levels and HRV are generally low, it is important to investigate the question whether regular physical activity can modify HRV in this age group.

In a randomised controlled trial, the effect of 6 months training on HRV was investigated in a group of 74 elderly. The training group gathered 3 times per week for a 45 minute supervised training session which consisted of aerobic, strength and flexibility exercises. At the end of the intervention period HRV was higher, primarily during the day. During daytime, the standard deviation of all normal intervals (+6%) as well as the low frequency component (+15%, LF) and the very low frequency component (+10%, VLF) of HRV were significantly increased ($P < 0.05$) in subjects of the intervention group as compared with the control group. Effects of training were most pronounced in subjects inactive in sport at baseline.

This study demonstrates that regular physical activity increases HRV (specifically in the very low and low frequency components) in elderly subjects. Hence, in elderly subjects, physical training is an effective means to positively modify a factor that is associated with increased incidence of cardiac events.

INTRODUCTION

Heart rate variability (HRV), the spontaneous fluctuations around the mean heart rate, is a simple non-invasive measure that reflects the autonomic balance. A reduced HRV is associated with increased incidence of total mortality and cardiac events in both post infarction patients,[1-3] and apparently healthy middle aged and elderly subjects.[4-6] It is assumed that a reduced HRV is a reflection of elevated sympathetic activity, a condition that may decrease the fibrillation threshold and thus predispose to ventricular fibrillation.[7] With increasing age the respiratory variation in heart rate decreases[8] and baroreceptor reflexes attenuate[9,10] and HRV is reported to be lower in elderly.[11]

It is widely presumed that regular physical activity induces adaptations in the autonomic nervous system. One of the possible adaptations is an increase in parasympathetic activity and HRV.[12-15] Until now, most intervention studies have been performed in chronic heart failure or myocardial infarction patients.[16-20] The majority of these studies report a considerable and significant increase in HRV after a period of physical training.[16,18-20] Only 2 studies have been performed in healthy middle aged and elderly subjects, using relatively short recordings. These show inconsistent results. Seals *et al.*[15] observed a 15% significant increase in HRV (standard deviation of RR-intervals of a 5 minute recording) at rest in healthy middle aged and elderly sedentary men, who followed a strenuous and prolonged endurance training programme. In contrast, Boutcher *et al.* [21] recently failed to show an increase in HRV in healthy middle aged men after a training period. However, this training protocol was shorter and of moderate intensity.

Since elderly have both increased incidence of cardiac events and a reduced HRV, it is important to learn more about the effects of regular physical activity on HRV in this age group. Therefore we have studied change in HRV, both in the time and frequency domain in elderly men and women who were randomly allocated to a 6 months' training programme or a control group, using 24 hour ECG recordings.

SUBJECTS AND METHODS

Subjects

The study population comprised Caucasian people, 60 to 80 years old, living in a middle sized city in the Netherlands. Participants took part in an intervention study which investigated the effect of a 6 months' training programme on various cardiovascular risk factors. The response rate of the intervention study was 38%. Participants were younger and were more active, in comparison with the refusers. In total, 74 elderly men and women, randomly recruited from intervention and control group, participated in the present study. These subjects complied with the following inclusion criteria: normal resting and exercise electrocardiogram, no myocardial infarction or stroke in the past 2 years, no insulin dependent diabetes mellitus, no heart failure, no unstable angina pectoris, and no use of beta blockers. Fourteen pre-intervention ambulatory electrocardiogram (ECG) recordings could not be used, due to bad quality tapes ($n = 12$), pacemaker ($n = 1$) and atrial fibrillation ($n = 1$). From the remaining 60 elderly subjects, 3 provided unsuitable post intervention HRV measurements, due to bad tape quality ($n = 2$) and atrial fibrillation ($n = 1$). One subject dropped out during the intervention period and 5 subjects were not able to do the post intervention ECG measurement, due to illness ($n = 3$) and holiday ($n = 2$). Therefore, we were left with a group of 51 elderly with an adequate pre- and post- intervention ECG measurement. All participants provided informed consent according to the guidelines of the Medical Ethical Committee of the Wageningen Agricultural University.

Ambulatory ecg recording

At the beginning and end of the intervention period, subjects were visited at home by the research assistant who attached the ECG electrodes, started the 3-lead Marquette 8500 Holter recorder (Marquette Electronics Inc. Milwaukee, Wisconsin) and instructed the participants how to disconnect the Holter recorder after 24 hours. The recorder was collected the next day.

Assessment of HRV

Signal processing. The electrocardiogram was analysed with a Marquette Series 8000 Holter Analyzer. Accurate determination of the onsets of the QRS-complexes was accomplished by an extensive review and edit procedure and a computer programme from the Marquette 8000 Holter research software modules. The resulting inter-beat interval series were further analysed on a personal computer[22].

Power Spectral Analysis. Frequency domain analysis was performed by calculating the power density spectrum, using the fast Fourier algorithm. We computed high frequency, (HF, 0.15-0.40 Hz), low frequency, (LF, 0.05-0.15 Hz) and very low frequency power, (VLF, 0.01-0.05 Hz) for every 5 minute interval[22].

Time domain analysis. The standard deviation of all normal RR intervals (SD-RR) and the percentage of differences between adjacent normal RR intervals exceeding 50 ms (pNN50) were calculated for every 5 minute interval (SD-RR).

Other characteristics

Maximal oxygen consumption (VO_2max) and maximal exercise capacity (Wmax) were determined in a maximal exercise test on an ergocycle before and after the intervention period. The protocol started with a load of 30 Watt for women and 60 Watt for men and every three minutes work load was increased with 30 Watt. We used this protocol in order to approach a steady state at each level, to be able to evaluate intercurrent ischemia. Body mass index was calculated as body weight (kg) divided by height squared (m^2). Smoking status was assessed during an interview.

Exercise protocol

The 74 elderly subjects who participated in this study were allocated to a training (n = 36) and a control group (n = 38). During half a year, subjects of the

training group gathered 3 times per week in a sports facility for a 45 minutes supervised training session. This training consisted of various activities, such as aerobic exercise (ball games, jogging, exercise to music), callisthenics and flexibility exercises. The instructor saw to it that the intensity of the training was adapted to the individuals capacity. The attendance in the all-round group was 72% for men and 81% for women. Subjects in the control group were asked to maintain their habitual activities during the 6 months' period, but were not restrained from undertaking (more) physical activity.

Data analysis

Means of SD-RR and pNN50 and arithmetic and geometric mean of HF, LF and VLF (all from 5 minute averages) were calculated for the complete 24 hour recording, during the active period of the day (between 6 am and 6 PM) and during sleep (between 2 and 5 am). General characteristics at baseline were calculated for all subjects with an acceptable Holter pre-intervention measurement.

Mean change in physical fitness (VO_2max, Wmax) and the various HRV measures in the intervention and control group were compared using Students t-test. To investigate the effect of the training programme in sedentary subjects, we repeated the analysis, including only subjects who were inactive in sport at baseline. In order to evaluate if changes in HRV parameters were affected by changes in physical fitness and mean heart rate, a regression analysis was performed, in which HRV parameters were dependent variates and assignment (intervention, control) and change in physical fitness and mean heart rate were independent variates.

The association between physical fitness (VO_2max and Wmax) and HRV, both baseline levels as well as change during the intervention period, were evaluated using regression analysis. In the baseline analysis, adjustment was made for sex, smoking and age.

RESULTS

In **Table 5.1** baseline characteristics of the study population are depicted, separately for subjects of the intervention and control group who had a fit-for-use pre intervention holter tape. Subjects in the intervention group were younger (*P*<0.05) and had a higher body mass index. About half of the elderly were already regularly active in sport at baseline. Subjects with a missing post intervention measurement (loss to follow up) did not significantly differ from subjects who completed the protocols with respect to age, body mass index, blood pressure or HRV characteristics at baseline.

Table 5.1. *Baseline characteristics of the study population (mean ± sd)*

	Intervention $n=27$	Control $n=24$	Loss to follow up $n=9$
General characteristics			
Age (years)	65.1 ± 4.7*	69.0 ± 4.8	67.9 ± 6.6
Body Mass Index (kg/m^2)	25.8 ± 3.8	24.0 ± 3.1	24.1 ± 2.0
Resting heart rate (b/m)	63.4 ± 7.3	63.5 ± 7.5	61.1 ± 7.3
Smoking (%)	25.9	25.0	11.0
Active in sport (%)	59.3	41.7	66.7

* $P < 0.01$ Students t-test intervention versus control group

The mean baseline SD-RR, LF and VLF, but not HF, were associated with the baseline fitness level (**Table 5.2**), however, after adjustment for sex, smoking and age, the association attenuated and became insignificant.

Table 5.3 shows the mean values of physical fitness and HRV at baseline and after the 6 months' training period for subjects who completed the protocols. Despite randomisation, mean values of baseline HF, SD-RR and pNN50 were lower in the intervention group as compared with the control group, although not statistically significant. After the intervention period, subjects of the training

group significantly increased both VO_2max as well as Wmax as compared to the control group.

Table 5.2. *The crude and adjusted association (regression coefficients) between physical fitness (independent variate) and HRV (dependent variate) at baseline.*

Heart Rate Variability	24 hr		sleep		day	
	crude	*adjusted‡*	*crude*	*adjusted*	*crude*	*adjusted*
SD-RR (10^{-3} sec)						
VO_2 max (ml/kg/min)	0.5*	0.2	0.6†	0.4	0.5*	0.3
Wmax (Watt/kg)	6.2*	3.4	7.9†	5.4	6.3*	4.2
log HF (10^{-3} sec^2)						
VO_2 max (ml/kg/min)	-2.1	-2.4	-4.8	-2.4	0.6	0.0
Wmax (Watt/kg)	-19.9	-18.4	-64.4	-28.0	18.3	16.6
log LF (10^{-3} sec^2)						
VO_2 max (ml/kg/min)	7.0†	0.4	9.4	3.2	5.9†	1.0
Wmax (Watt/kg)	115.2*	44.2	129.0†	61.0	105.7*	56.8
log VLF (10^{-3} sec^2)						
VO_2 max (ml/kg/min)	5.6†	1.5	5.6	-1.9	5.3*	3.0
Wmax (Watt/kg)	78.9*	28.9	73.5	-9.1	76.6*	46.1

SD-RR Standard deviation RR interval, HF = high frequency (0.15-0.40 Hz), LF = low frequency (0.05-0.15 Hz), VLF = very low frequency (0.01-0.05 Hz),
VO_2max = maximal oxygen consumption, Wmax = maximal exercise capacity.
* $P<0.05$, † $0.05 < P<0.1$
‡ adjusted for sex, smoking (yes,no) and age

The mean SD-RR and pNN50 of the total 24-hour recording were modestly increased in the intervention group (5% and 13% respectively), whereas the control group showed a small decrease (*P*-value of difference: 0.11 and 0.32). The average changes in 24-hour HF, LF and VLF were positive in the intervention group and negative in the control group, however rather small and not significantly different between intervention and control group. During the day (between 6 am and 6 PM), mean increase in SD-RR, pNN50, LF and VLF in subjects of the intervention group was more pronounced (6%, 16%, 15% and

Table 5.3. Pre and post intervention values of physical fitness and HRV (during 24 hour and the day) of subjects in the intervention and control group (n=51).

	INTERVENTION		CONTROL	
	before mean ± SD	after mean ± SD	before mean ± SD	after mean ± SD
Physical fitness				
VO_2max (ml/kg/min)	27.9 ± 8.3	30.3 ± 7.8*	24.7 ± 8.3	25.2 ± 6.7
Wmax (Watt/kg)	2.12 ± 0.69	2.31 ± 0.69*	1.83 ± 0.57	1.89 ± 0.57
24 hour ECG				
Heart rate (b/min)	73.2 ± 7.1	72.0 ± 7.7	71.6 ± 7.6	70.1 ± 6.9
SD-RR (10^{-3} sec)	45.6 ± 11.6	48.0 ± 11.0	49.3 ± 13.9	48.9 ± 12.8
pNN50 (%)	3.8 ± 3.4	4.3 ± 4.0	7.4 ± 9.2	6.9 ± 8.1
HF (10^{-3} sec^2)	0.28 ± 0.35	0.27 ± 0.19	0.40 ± 0.43	0.39 ± 0.39
LF (10^{-3} sec^2)	0.61 ± 0.38	0.66 ± 0.38	0.62 ± 0.29	0.60 ± 0.32
VLF (10^{-3} sec^2)	1.31 ± 0.54	1.41 ± 0.56	1.35 ± 0.51	1.31 ± 0.50
day ECG				
Heart rate (b/min)	77.0 ± 7.6	75.2 ± 9.1	75.0 ± 8.0	73.8 ± 8.0
SD-RR (10^{-3} sec)	46.4 ± 10.7	49.3 ± 11.6*	50.3 ± 12.2	47.5 ± 11.1
pNN50 (%)	3.1 ± 2.7	3.6 ± 3.8	6.2 ± 7.3	5.6 ± 6.4
HF (10^{-3} sec^2)	0.27 ± 0.29	0.25 ± 0.14	0.40 ± 0.39	0.34 ± 0.34
LF (10^{-3} sec^2)	0.62 ± 0.30	0.71 ± 0.42*	0.64 ± 0.27	0.54 ± 0.23
VLF (10^{-3} sec^2)	1.37 ± 0.53	1.50 ± 0.61*	1.44 ± 0.49	1.28 ± 0.40

SD-RR=Standard deviation RR interval, pNN50=percent of difference between adjacent normal RR intervals > 50 ms, HF=high frequency (0.15-0.40 Hz), LF=low frequency (0.05-0.15 Hz) VLF=very low frequency (0.01-0.05). VO_2max=Maximal oxygen consumption, Wmax=maximal exercise capacity, * $P<0.05$, difference in mean change between intervention and control group.

10%) and, except for pNN50, significantly different from the control group ($P=0.02$, $P=0.32$, $P=0.05$ and $P=0.02$, respectively). Mean change in HRV characteristics between 7 am to 7 PM or between 8 am to 8 PM showed similar results.

When the analysis was restricted to subjects who were inactive in sport at baseline ($n=25$), a larger increase in HRV in the intervention group was observed. Mean increase in 24-hour SD-RR, LF, VLF were 11%, 42% and 20%, with P-values for the difference with the control group of 0.08, 0.03 and 0.04 respectively. Again, among the elderly of the intervention group, increase in HRV was most pronounced during the day (SDRR: $+17\%$, $P<0.01$, pNN50: $+104\%$, $P=0.08$, HF: $+40\%$, $P=0.09$, LF: $+54\%$, $P<0.01$, VLF: $+31\%$, $P<0.01$).

Change in SD-RR and HF were significantly associated with a change in heart rate (crude: -0.98 and -0.015 (10^{-3} sec^2) per 1 beat/min respectively), but not with change in VO$_2$max, or Wmax. However, the difference in change of the HRV parameters between intervention and control group was not attenuated after adjustment for changes in heart rate.

DISCUSSION

In a randomised intervention study, we studied the effect of a 6 months' training programme on heart rate variability, a characteristic of autonomic nervous function, from 24 hour ambulatory ECG recordings of an elderly population. Subjects in the intervention group showed a small increase in total 24-hour HRV (SD-RR) and in the very low and low frequency component (VLF, LF), but a moderate and significant increase in daytime-HRV, compared with the control group, in which a small decrease was observed. The differences were most pronounced and significant among subjects who were sedentary at baseline and independent of change in mean heart rate.

Increasing HRV may be important, since low HRV, particularly common in elderly, was recently observed to be associated with increased incidence of cardiac events and total mortality in a healthy population.[4-6] All HRV measures in the time and frequency domain were associated with increased risk of

cardiac events (angina pectoris, myocardial infarction, coronary heart disease death or congestive heart failure). One standard deviation decrement in log SD-RR was associated with a relative risk of 1.5 (95% confidence interval 1.2 to 1.9). One standard deviation decrement in log LF was associated with a 1.7 times greater hazard of total mortality.

The observed small reduction in HRV among subjects in the control group may be caused by a reduction in physical activity during the intervention period. The study was conducted during the winter months, in order to have a lower level of background physical activity and to minimise absence at the training sessions due to holidays. Also our control subjects had spent less time on walking (-65 minutes per week), and gardening (-3.5 hour per week), but not on sports or bicycling, than during the summer.

Methodological issues

Since baseline levels of some HRV measures (SD-RR, HF and especially pNN50) were somewhat different between intervention and control group, regression towards the mean in these parameters can not be ruled out. It remains unclear to what extent this phenomenon may have affected the results of the study.

The ambulatory ECG measurement may have been subject to possible errors. As has been mentioned before, a large proportion of the tapes were of insufficient quality (11%). We believe that these missings were random, since it was caused by bad signal conduction and (except for 2) not by abnormalities in the ECG.

Unlike the short term standardised recording performed in a laboratory, the 24 hour Holter recording enables studying of HRV under natural conditions, and during wake and sleep. Differences in physical activity pattern during Holter recording might hamper comparability between intervention and control group. However, participants were instructed not to have exercise during the measurement, and since the Holter recorder discouraged undertaking other strenuous activities, it is not likely that the activity pattern was materially different between intervention and control group, nor within the groups during

pre- and post-intervention measurements. Still, differences can not be completely ruled out.

Other intervention studies

The majority of intervention studies investigating the effect of physical training on HRV has been performed in heart patients[16-20] and most of these studies have observed significant and considerable increases in HRV. However, to our knowledge, only 5 studies have reported the effect of regular exercise during longer periods on HRV in healthy subjects. Three of these were carried out in young and 2 in middle aged and elderly subjects. The studies performed in young subjects show an increase in SD-RR[23] and LF[23,24] of about 26%. The change reported in HF was inconsistent, 2 studies reported an unexpected decrease in HF in the range of 12-60%,[23,24] whereas 1 observed a significant increase in HF in 9 of the 11 individuals who followed a 6 week intensive training programme.[25]

The studies performed in middle aged and elderly show inconsistent results. Seals *et al.* observed a moderate increase of 15% in SD-RR after 30 weeks of training, while Boutcher *et al.* did not find any effect after a moderate training programme of only three months. The training effect we observed in our study is similar to the results of Seals *et al.*[15] The results so far, may suggest that training modulates HRV beneficially, only when it is performed vigorously enough.

Until now, most training intervention studies in healthy subjects and patients have used short term ECG recordings. Those who have reported an effect, obviously found it during the day. Only one study has performed a 20 hour recording in congestive heart patients (16), but also in this study increase in HRV (in the high frequency domain) was observed only during the day. Our results are in line with these studies. We do, however, not have an explanation for this, other than a greater challenge to circulatory homeostasis during the day.

Interpretation

It is generally assumed that HRV is a measure of parasympathetic activity. Therefore, increase in HRV in subjects of our intervention group may reflect increase in parasympathetic activity. Such a training induced parasympathetic increase may counteract the increased sympathetic activity with advancing age and, thus, reduce the risk of myocardial ischemia and fatal arrhythmias.[1] Still the interpretation of training adaptations in the various frequency domain components remains unsolved. However, if the association between physical activity and HRV on the one hand, and the association between HRV and incidence of cardiac events, on the other, is confirmed by other studies, physical activity may have preventive implications.

In conclusion, a 6 months' intensive training programme resulted in a moderate increase in heart rate variability, primarily during the day, among a group of elderly in both time domain (SD-RR) as well as frequency domain (VLF, LF). Hence, in elderly subjects, physical training is an effective means to positively modify a factor that is associated with increased risk of cardiac events.

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CHAPTER 6

The effect of regular activity on symptoms of depression and physical self-efficacy in elderly: Comparison between two exercise protocols

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ABSTRACT

The effects of regularly performed exercise during 6 months on symptoms of depression and physical self-efficacy were assessed in elderly men and women. The subjects were randomly allocated to (a) a supervised group exercise programme, comprising various activities (b) an individually performed exercise-bicycle programme at home and (c) a control group. Symptoms of depression were assessed using the Centre for Epidemiologic Studies Depression Scale (CES-D), physical self-efficacy was assessed using a sub-scale of the Self-Efficacy Scale, so-called Dutch LIVAS-scale.

After 6 months, symptoms of depression were reduced in men and women of the intervention group, but this reduction was not significantly different from the control group and could therefore not be attributed to the intervention programme. However, the CES-D item 'experiencing depressive mood in the past week' was significantly less common in elderly people of the group exercise programme ($P < 0.05$). In addition, after the intervention, physical self-efficacy was increased in both intervention groups as compared to the controls, but particularly in the all-round group exercise programme. Change in CES-D was significantly associated with change in LIVAS (beta -0.27 unit increase LIVAS per 1 unit increase of CES-D, SE 0.11).

In conclusion, these data indicate that regular physical activity may positively affect physical self-efficacy, in particular among elderly following an all-round activity programme. It may be speculated that increase in physical self-efficacy, in combination with the social aspects of group exercise may (ultimately) lead to a reduction in occurrence of depressive symptoms in elderly.

INTRODUCTION

Cross-sectional and longitudinal studies have shown an inverse relationship between regular physical activity and symptoms of depression in elderly, independent from health and socio-economic status.[1-4] It was suggested that physical self-efficacy (defined as self-efficacy related to physical status and functioning) may act as a potential mediator in this relationship.[5] However, the design of these studies did not allow conclusions about the temporality of this association. Physical activity may affect physical and psychological well-being, or it may be the other way around, well being may influence the amount of physical activity.

Intervention studies, investigating the effect of training on physical self-efficacy, although only few in number, seem to report consistent beneficial effects.[6,7] The effects of training on symptoms of depression, however, remain inconclusive.[8-14] Some studies report beneficial effects,[12-14] whereas others do not find any effect[8-11] of physical training. It also remains unclear, whether it is the exercise itself or the social component causing changes in depressive symptoms.

Insight into the effects of exercise training on depressive symptomatology and physical self-efficacy may be important, since advancing age is associated with functional losses and dependency, which may have a great impact on both physical and psychological well-being.[15] Prevalence of depressive symptoms in the Dutch elderly population is estimated to be 9% in men and 16% in women.[16]

We studied the effects of regularly performed exercise on depressive symptomatology and physical self-efficacy in a group of Dutch elderly men and women randomly assigned to either (a) group exercise programme, the so-called all-round activity group (b) an individually performed exercise bicycle programme and (c) a control group. This way we were able to compare the effects of individual and groupwise exercise.

SUBJECTS AND METHODS

Subjects

The study population consisted of apparently healthy elderly people, aged 60 to 80. Subjects were asked, via their general practitioner, to participate in an intervention study investigating the effects of 6 months exercise training on cardiovascular risk factors. 152 men and 166 women volunteered. Compared with refusers, these volunteers were slightly younger (men: 68,5 ± 5,5 vs 71,5 ± 5,6, women 67,8 ± 5,4 vs 70,5 ± 5,4), and less often considered themselves inactive as compared to peers (men 49% vs 77%, women 48% vs 77%). All volunteers provided informed consent and the study was approved by the Medical Ethical Commitee of the Agricultural University Wageningen.

Volunteers were screened to make sure they were fit to participate in a physical exercise programme. Subjects with hypertension or abnormalities in resting or exercise electrocardiogram were excluded from the study (39 men and 50 women). This left us with a study population of 113 men and 116 women.

Participants were randomly assigned to an exercise bicycle group (48 men and 48 women), an all-round activity group (25 men and 22 women) or a control group (40 men and 46 women). During the intervention 12 men and 19 women prematurely stopped with the bicycling programme, 5 men and 5 women withdrew from the all-round activity group and 2 men and 2 women withdrew from the control group. Main reason for withdrawal from the exercise bicycle group were medical problems (50%) and lack of motivation (40%), while subjects in the all-round activity group withdrew primarily because of time restraints (70%). Primary reason for withdrawal from the control group were family circumstances.

Training

Elderly in the exercise bicycle group trained on an exercise bike, four times a week during half a year. Exercise sessions consisted of 30 minutes of continuous bicycle ergometry at an equivalent to 70% of their maximal exercise capacity (Wmax), which was individually determined in the baseline maximal exercise test. Adherence to the bicycle protocol was on average 86% for men and 81% for women of the prescribed training sessions. Subjects of the all-round activity group gathered 3 times a week for a 45 minutes training session, led by an experienced sports instructor, during half a year. The training consisted of aerobic exercise, callisthenics and flexibility exercises. The attendance in the all-round activity group was 72% for men and 81% for women. Subjects in the control group received no intervention and were asked to maintain their habitual activities during the intervention period, but undertaking more physical activity, if desired, was not discouraged

During the intervention period, subjects from both intervention and control groups were bimonthly contacted by telephone for an interview and twice invited for information evenings and social meetings.

Depressive symptoms

Depressive symptomatology was assessed using a Dutch translation of the Centre for Epidemiologic Studies Depression Scale (CES-D),[17] which proved to be a valid instrument in older adults.[16] The scale consists of 20 items, which inquire about the frequency of experiencing a given symptom during the previous week on a scale ranging from 0 (rarely or none) to 3 (most or all of the time). Items emphasise lack of energy, loneliness and negative self image. The summation of the component scores provides a total score, ranging from 0 to 60, with high scores suggesting greater severity and number of symptoms. A cut-off score of 16 was used to identify respondents with levels of depression which are clinically relevant.[16]

Physical self-efficacy

Physical self-efficacy was measured using the so-called 'LIVAS'-scale, a Dutch translation[18] of the *Perceived Physical Activity Scale*, which is a sub-scale of the *Self-Efficacy Scale*[19]. It was adapted for the use with elderly persons by replacing the category 'running' by 'going up and down the stairs'. Before the intervention, physical self-efficacy was determined by 10 questions asking subjects to evaluate their physical capacities compared to other people of their own age on a 5 point scale. After the intervention, physical self-efficacy was determined by the same questions, but this time subjects had to evaluate their physical capacities as compared to these at the beginning of the intervention. The total score is a summation of the individual items. Higher scores indicate higher physical self-efficacy. The score ranges from -20 to 20. The LIVAS-scale has been shown to be a valid tool to assess physical self-efficacy at old age.[20]

Data analysis

Change in CES-D and LIVAS was compared between intervention groups and control group using Dunnetts t-test or Students t-test. The association between change in CES-D score and LIVAS score was investigated using univariate regression analysis. All data-analyses were performed with SAS 6.09 (Statistical Analysis System; SAS Institute Inc. Cary, USA).

RESULTS

Baseline characteristics and associations

Table 6.1 shows the baseline characteristics of the subjects who completed the protocols. Subjects in the all-round activity group were younger than the controls, but no significant differences were observed in CES-D and LIVAS score between the groups. The prevalence of depressive symptoms as assessed by a CES-D score of 16 or higher was 3.5% in men and 7.8% in women, which

was lower than in the general Dutch population.[16] Mean (± SD) CES-D score in women (8.1 ± 5.6) was significantly higher (*P*<0.05) than in men (6.6±4.0), whereas LIVAS score was significantly lower (6.1±5.6 and 7.6±5.2 respectively). Women who were already engaged in sport activity at baseline had a significantly higher LIVAS score (7.7±5.5 vs 4.7±5.4) and a markedly, although borderline significantly lower CES-D score (7.2±3.1 versus 9.0±6.9). In men, the same trend was observed for LIVAS score (8.5±5.2 vs 7.0±5.1, not statistically significant) but the CES-D scores were similar among those who were and were not already active in sport (6.6±4.0 and 6.7±4.0 respectively). Differences were independent of age and presence of musculo-skeletal diseases. Earlier cross-sectional studies also reported a stronger inverse association between physical activity and depressive symptomatology in women than in men.[1,2] The difference between men and women may be partly a consequence of the fact that men had more difficulties in expressing their feelings, resulting in an underestimation of prevalence of depressive symptoms. A gender bias in the CES-D scale has been suggested earlier.[21]

Table 6.1. *Baseline characteristics* of the study population*

	Bicycle		All-round		Control	
	men	*women*	*men*	*women*	*men*	*women*
	n = 36	n = 28	n = 19	n = 16	n = 38	n = 44
Age (y)	68.3 ± 5.2	68.1 ± 5.5	66.1 ± 4.7	64.1 ± 4.2	69.1 ± 5.8	69.0 ± 5.1
CES-D score	7.6 ± 0.9	6.9 ± 0.8	5.7 ± 0.8	8.4 ± 1.4	6.1 ± 0.5	7.2 ± 0.6
LIVAS score	7.7 ± 4.9	7.0 ± 4.9	8.4 ± 4.9	7.3 ± 6.7	7.2 ± 5.7	6.5 ± 5.8
Perceived health[@]	7.7 ± 1.0	7.9 ± 1.1	7.3 ± 1.0	7.9 ± 1.0	7.6 ± 1.2	7.8 ± 1.1
Active sport(%)	41.7	50.0	63.2	62.5	29.0	45.5

* mean ± sd, or percentage

[@] score: range 0 (very bad) to 10 (excellent)

Intervention effects

Table 6.2 shows the observed changes in CES-D scores and post intervention LIVAS scores, separately for men and women of the intervention and control group. Symptoms of depression according to the CES-D score were reduced in men and women of the intervention groups, but this decline was not significantly different from the change in the control group, and could therefore not be attributed to the programme. The expected greater improvement in CES-D score among subjects in the all-round activity group, based on its social component, did not occur. However, the CES-D item 'have you experienced a depressive mood in the past week' was, significantly lower after the intervention period in men and women of the all-round group as compared with the controls (*P*<0.05, Students t-test).

Other intervention studies investigating the effect of training on symptoms of depression have shown inconsistent results. Some studies reported improvement of symptoms of depression in elderly,[12-14] whereas other studies fail to show any changes.[8-11] In general, beneficial effects of training were particularly observed in subjects who initially had depressive symptoms. Our study population was healthier and had less depressive symptoms than a general elderly population and training effects may have therefore been smaller.

Table 6.2. *Change[#] in CES-D score and LIVAS score after 6 months intervention*

	Bicycle		All-round		Control	
	men n = 36	*women* n = 28	*men* n = 18	*women* n = 16	*men* n = 37	*women* n = 43
CES-D	-2.2 ± 1.3	-2.5 ± 1.2	-2.4 ± 0.8	-1.6 ± 1.1	-2.8 ± 0.9	0.2 ± 1.0
LIVAS	2.6 ± 0.7*	2.5 ± 0.8*	4.9 ± 0.8*	6.9 ± 1.3*	-0.1 ± 0.3	-0.1 ± 0.3

[#] mean ± standard error
* P < 0.05 Dunnett t-test intervention groups versus control group

Physical self-efficacy was markedly increased among subjects of the intervention groups, and particularly elderly of the all-round activity group, as compared to the controls ($P<0.05$). Elderly people of the intervention groups perceived an increase in strength, flexibility, speed of response and fitness ($P<0.05$, component-items of the LIVAS questionnaire). Our results hereby confirm previous reports.[6,7]

As suggested by others,[5] change in depressive symptoms was significantly associated with change in physical self-efficacy. Increase in 1 unit of LIVAS was associated with a reduction of -0.27, (SE 0.11) units in CES-D within the total group. For women this association was stronger than in men (beta: -0.39 ± 0.15 and -0.11 ± 0.17 (not significant) respectively). Again, the gender difference might be explained by the CES-D questionnaire being a less valid instrument in men than women.

CONCLUSIONS

These data show that regular physical activity enhanced physical self-efficacy of the older individual, particularly among elderly who followed group training sessions consisting of an all-round exercise programme. Elevated physical self-efficacy may lead to a reduction in depressive symptoms, by facilitating independence and a higher quality of life. Although our study could not demonstrate significant changes in CES-D score, 'experiencing a depressive mood during the past week' was significantly lower in the subjects who followed group training sessions. This study suggests that exercise training in general, but group training consisting of an all-round exercise programme in particular, should be recommended to elderly people.

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CHAPTER 7

Validity of the Physical Activity Scale for the Elderly (PASE) according to energy expenditure assessed by the doubly labelled water method

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ABSTRACT

The study investigates the validity of the Physical Activity Scale for the Elderly (PASE) in 21 Dutch elderly men and women. The PASE is an easily scored, brief questionnaire for elderly, suitable for large epidemiological studies. The PASE-score was compared with physical activity measured with the doubly labelled water method.

The correlation coefficient of the PASE-score with the residuals from the regression analysis using total energy expenditure as dependent and resting metabolic rate as independent variate was 0.58 (95% CI: 0.50-0.81). Women had greater engagement in extremely high scoring activities as housework and taking care of others, resulting in higher PASE-scores than men (97.9 and 71.9). The higher scores in women were not linked to higher activity levels, which suggests that the mentioned activities may be overvalued. Sex specific correlation coefficients were 0.79 (CI: 0.32-0.95) and 0.68 (CI: 0.15-0.90) for men and women respectively.

In conclusion, the PASE proved to be a reasonable valid method to classify healthy elderly men and women into categories of physical activity. Some possible refinements were suggested, which may improve accuracy of the PASE questionnaire.

INTRODUCTION

Epidemiological studies, investigating the effect of physical activity on health, often use questionnaires to assess physical activity. Questionnaires are cheap, not labour consuming and if valid are a very useful tool to assess physical activity in a general population. Validity of questionnaires is usually examined with pulse records,[1] motion sensors or accelerometers.[2-4] Food intake[1,2,5] or cardiorespiratory fitness and body composition[3] are used as proxies as well. The doubly labelled water (DLW) method, is considered as the golden standard in measuring energy expenditure in free-living subjects.[6,7] However, costs of this method are considerable and it is used only in small scale studies.

We assessed the validity of the Physical Activity Scale for the Elderly (PASE) developed by The New England Research Institute,[8] using the doubly labelled water method. The PASE was used to monitor changes in physical activity among elderly participating in an controlled intervention study, which investigated the cardiovascular response to regular physical activity. The PASE is designed to assess activities commonly engaged in by elderly persons. It assesses the activity of the past week, enabling detection of changes in activity over a relatively short period of time. The questionnaire does not estimate energy expenditure, like most questionnaires do, but produces a score with which subjects can be compared.

However, the questionnaire was designed for American elderly, who have a slightly different life style compared to Dutch elderly. We therefore adjusted the PASE questionnaire and we tested its validity among 21 elderly men and women with the doubly labelled water method.

SUBJECTS AND METHODS

Subjects
The subjects of this study were recruited from the participants of an intervention study, which was four months underway. The participants were residents of Arnhem, a middle sized city in the Netherlands. All elderly, age range 60 to 80 years, met the inclusion criteria for the intervention study: no

heart failure, no angina pectoris, no insulin dependent diabetes mellitus, no use of beta-blockers, and no myocardial infarction or stroke in the past 2 years. Subjects taking diuretic drugs, that could influence hydration, were excluded from the study, as this might influence the DLW measurement. At the entrance of the intervention study, the PASE questionnaire was administered among all participants. Based on tertiles of the PASE-score, the total population was stratified in low, middle and high activity groups, men and women separately. From each of these groups, subjects were selected, in equal numbers from intervention and control group, 22 in total. Thus a broad range of activities could be expected. Three subjects refused participation because of time restraints, therefore a peer from the same group was approached. One man dropped out a few days before the study started, leaving us with 10 men and 11 women. Subjects of the intervention group gathered 3 times a week for 45 minutes for performing aerobic exercise, callisthenics and flexibility exercises.

Measurements

The validity of the PASE was assessed by comparing the PASE-score with two measures of physical activity, namely (1) the physical activity ratio (PAR) which is the ratio of total energy expenditure (TEE) and resting metabolic rate (RMR) and traditionally and widely used and (2) the residual of the regression with TEE as dependent and RMR as independent parameter, as was recently recommended.[9] TEE was measured with the doubly labelled water method over a two week period and RMR was measured with a ventilated hood. Since change in body weight may affect the TEE measurement, body weight was measured before and after the measurement period. The PASE questionnaire was administered in the second week of the energy expenditure measurement with the doubly labelled water method.

The PASE questionnaire
The PASE questionnaire is a brief, easy tool for the assessment of short term physical activity in epidemiological studies of elderly. It comprises activities commonly engaged in by elderly persons, and does not emphasise sport and

recreational activities, as do most other questionnaires. Also, the reference period is shorter (one week) than other questionnaires. The rationale for this is that elderly generally have more problems recalling activities of a long time ago and that elderly are prone to changes in activities due to problems with physical or mental well being. A drawback, however, is that a single PASE score does not always reflect habitual activity. It is very liable to external influences such as weather conditions. Sitting activities, walking, cycling, recreational and sport activities (divided in light, medium and heavy) are recorded as never, seldom (1-2 days/week), often (3-4 days/week) and mostly (5-7 days/week). Duration is categorised in less than 1 hour, between 1 and 2 hours, between 2 and 4 hours and more than 4 hours per week, with exception of paid/unpaid work, which is recorded in total hours per week. Housework (light and heavy), lawn work, home repair and gardening and caring for others are recorded as either performed or not, so no frequency or duration is asked. The total PASE-score can be computed by multiplying the amount of time spent in each activity (hr/week) by the item weights and summing up all activities. The item weights are originally based on comparison with physical activity estimated with 3-day motion sensor counts, 3-day physical activity diary and global activity assessment[8].

Modification of the PASE

The PASE questionnaire was slightly adjusted for use in Dutch elderly. Bicycling is a very common activity among elderly in the Netherlands, both for transportation and for recreational purposes. We therefore added bicycling for transportation to the question in which time spent on walking was asked. We considered this legitimate, since walking and bicycling have similar metabolic values[10]. Brisk walking and bicycling for recreational purposes were listed among moderate sport and recreational activities, as was done in the original version of the questionnaire. The PASE divides gardening in heavy lawn work and outdoor gardening. In the category heavy lawn work, we added digging and working in a vegetable garden. Finally, morning gymnastics (stretching with some light strength training) was added to the light sport and recreational activities

Total energy expenditure by DLW

Total energy expenditure over a two week period was measured with the DLW method using the Maastricht protocol[11]. Comparing this technique with calorimetry[7,8] showed that it provided high levels of accuracy and precision (4-6%) in a wide range of subjects. A great advantage of this method is that it measures energy expenditure over a 2 week period and does not interfere with a subjects' usual activity.

In our study, all subjects were visited at home between 9.00 and 11.00 PM to collect a background urine sample, before the isotope dose was administered. Every subject received a dose according to their total body water. The dose consisted of 10 At% H_2 ^{18}O and 5 At% ^2H_2O resulting in an initial excess body water enrichment of 150 ppm for ^2H and 300 ppm for ^{18}O, leaving a sufficient excess enrichment at the end of the 2 week observation period. The subjects drank the labelled water straight from the bottle (with a straw). The bottle was rinsed with some tap water, which was consumed as well. The next day, one week later and two weeks later, urine was collected before 9.00 AM (the second voiding of the morning) and between 9.00 and 11.00 PM. The urine was sampled and stored at -20° C on the day of collection. Urine samples were analysed with isotope ratio mass spectrometry (Aqua Sira, VG, UK). ^{18}O was measured in water vapour, produced by on-line vacuum distillation, ^2H was measured in hydrogen gas, produced on-line by hot uranium technique[12].

Resting metabolic rate

Just before the start and at the end of the two week study period subjects were brought to the laboratory of Wageningen Agricultural University before 9.00 AM, after an overnight fast. Resting metabolic rate was measured by indirect calorimetry,[13] using an open-circuit ventilated hood system. The transparent hood with an air inlet on top and an air outlet at the right side was placed over the head of the subject. Through the hood, fresh filtered outside air was drawn by a pump (SCL210, Ocean, Dieren, The Netherlands). The air flow was measured by a thermal mass flow meter (5812N, Brooks, Veenendaal, The Netherlands) and maintained at 40 L/min by a control valve (5837, Brooks). Gas analyses were performed with, respectively, an infrared carbon dioxide analyser (1410, Servomex, Zoetermeer, the Netherlands) and a paramagnetic oxycon

analyser (1100A, Servomex). Dried standard gas and dried filtered fresh atmospheric air were used to calibrate the analysers. The span point of the oxygen analyser was controlled and was recalibrated every 60 minutes. Flow rate, carbon dioxide and oxygen concentrations were integrated over 2-minute intervals. Metabolic rate was calculated using Weir's equation[14]. Periodical alcohol combustion was used as a reference to which all measurements were standardised. The reproducibility of the ventilated hood measurements was determined by six alcohol combustion tests for each ventilated hood, carried out on separate days over two weeks (average RQ: 0.655, SD 0.015). The measurement was done under standardised conditions, with the subjects lying half supine in a thermoneutral room (temperature 21, SD 2 °C) and watching non stressing movies. The subjects were instructed to avoid heavy physical activity on the morning of the measurement. Subjects were asked to remain awake and motionless during the measurement. Metabolic rate was measured continuously for 60 minutes, but the mean energy expenditure of the last 45 minutes were used as the RMR. The 14 days within-person variation of RMR was 3.3% for women and 3.7% for men. For the data-analyses mean RMR was used

Body composition
Body mass was measured at the beginning and end of the study period, to the nearest 0.05 kg using a digital scale (ED60-T; Berkel, Rotterdam, The Netherlands), after voiding, with subjects wearing only light underwear. Body mass index was calculated as body weight (kg) divided by height (m) squared. Total body water (TBW) was measured with deuterium dilution, using a 10 hours equilibration interval. Previous research showed that this method had no significant differences with underwater weighing (mean difference: -1.1% ± 0.7%)[11]. Fat free mass was calculated as TBW divided by 0.732. Body fat was calculated as body weight minus fat free mass.

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DATA ANALYSIS

Mean values of age, body mass index and percentage body fat derived from the deuterium dilution technique, were calculated for men and women separately. For each subject, the PASE score was calculated and mean values for men and women were computed. To assess the contribution of each activity-item, we calculated the mean time expenditure per activity in the total group and multiplied the mean with the item weight. A regression analysis was performed in men and women combined, with energy expenditure as dependent and resting metabolic rate as independent variate, to calculate the residuals. The residuals represent the difference of the actual value with the predicted value of energy expenditure, according to RMR. A negative residual indicates that a subjects' energy expenditure was lower than would be expected by the regression model, which is based on the total group. The correlation of PAR and residual with the PASE score were calculated. Because of non-normality of the PASE-score, Spearman correlation coefficients were used.

RESULTS

Table 7.1 shows the baseline characteristics of the study population. Men were slightly older and had a lower PASE-score than women. The higher PASE-score of women was mainly due to a more frequent participation in heavy housework (8 vs 1) and taking care of others (3 vs 0) (for relative contribution of activities to the PASE score see **Table 7.2**). Although PAR was similar for men (1.78 ± 0.22) and women (1.85 ± 0.23), women had lower residuals in the regression analysis with TEE (MJ/day) as dependent and RMR (MJ/day) as independent variate (**Figure 7.1**). The regression line had an intercept of 4.08 (SE = 1.4), and a beta for RMR of 1.11 (SE = 0.23).
Table 7.2 gives an overview of the various activities included in the PASE-questionnaire. For each activity, average time expenditure or proportion of participants involved, item weight and contribution to the mean PASE score are presented, for men and women combined. In our population, walking, cycling and light housework were the major components of the PASE-score.

Table 7.1. *Baseline characteristics (mean and sd) of the participants*

	MEN (n = 10)		WOMEN (n = 11)	
	mean	sd	mean	sd
Age (years)	70.6	3.8	69.2	4.8
Body mass index (kg/m2)	26.3	2.2	24.3	3.0
Body fat (%)	29.5	0.5	34.4	5.4
PASE-score	71.9	26.8	97.9	45.9
number of smokers	1		1	
cigt/week	175	0.0	175	0.0
number of alcohol consumers	8		5	
drinks/week	3.0	1.1	2.2	1.6
subjects active in sport	7		7	
min/week	270.0	155.9	244.3	92.4

Table 7.2. *PASE activities, performance, weight score, and contribution to the PASE-score of the total group*

PASE activity	performance	item weight	contribution PASE
Walking & bicycling	1.10 hr/day	20	22.0
Light SRA*	0.08 hr/day	21	1.68
Moderate SRA	0.12 hr/day	23	2.76
Heavy SRA	0.19 hr/day	23	4.37
Muscle strength/endurance	0.0 hr/day	30	0
Paid/unpaid work	0.30 hr/day	21	6.3
Light housework	95.2 %	25	23.8
Heavy housework	42.9 %	25	10.73
Home repairs	9.5 %	30	2.85
Lawn work	9.5 %	36	3.42
Gardening	4.8 %	20	0.96
Caring for others	19.0 %	35	6.65
Total activity		PASE-score	85.5

SRA = Sport and Recreational Activities

Figure 7.2 shows a plot of the significant correlation between the PASE-score and PAR ($P<0.01$). The Spearman correlation coefficient between PAR and PASE-score was for the total group 0.68 (95% CI: 0.35-0.86), for men 0.78 (95% CI: 0.31-0.95) and women 0.59 (95% CI: 0.00-0.88). Figure 7.3 shows a plot of the PASE score with the residuals of the regression TEE=RMR. The Spearman correlation coefficient of the PASE-score with the residuals of the regression analysis was 0.58 (95% CI: 0.50-0.81) in the total population and statistically significant. For men and women separately it was 0.79 (95% CI: 0.32-0.95) and 0.68 (95% CI: 0.15-0.90) respectively. Both Figure 7.2 and 7.3 show that PASE can distinguish into categories of physical activity, but the outliers show that PASE does not reflect exactly actual metabolic activity. Figure 7.3 clearly shows an overestimation of PASE-scores in women as compared to men, indicating that sex specific activities like housework and taking care of others may be overvalued in the PASE score.

Figure 7.1. Regression analysis with RMR as independent and TEE as dependent variate.

$y = 4.08 + 1.11x$
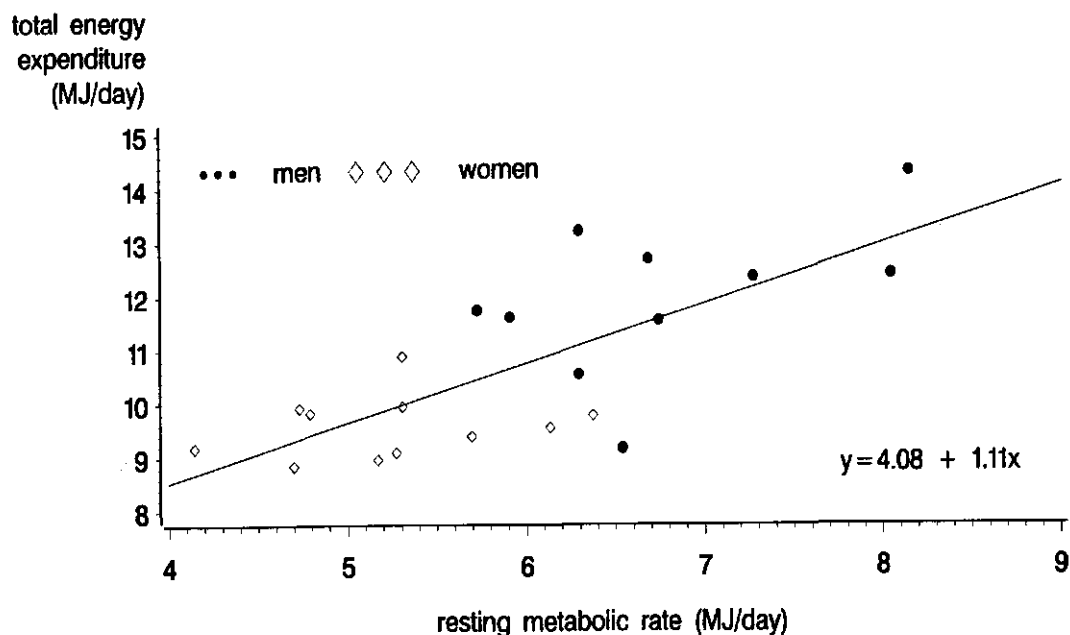
Figure 7.2. Correlation between PASE score and PAR.
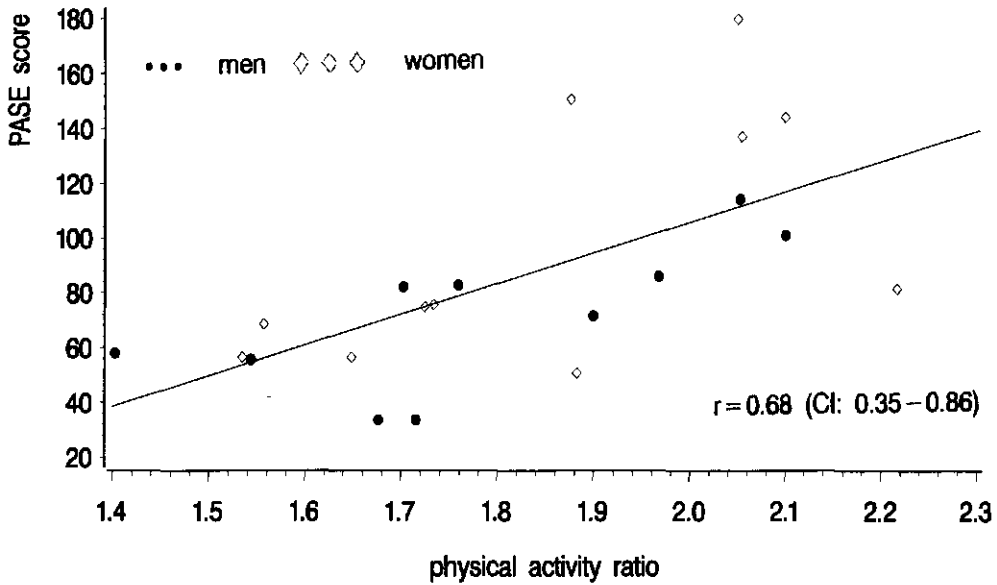
Figure 7.3. Correlation between PASE score and residuals of regression with RMR as independent and TEE as dependent variate.
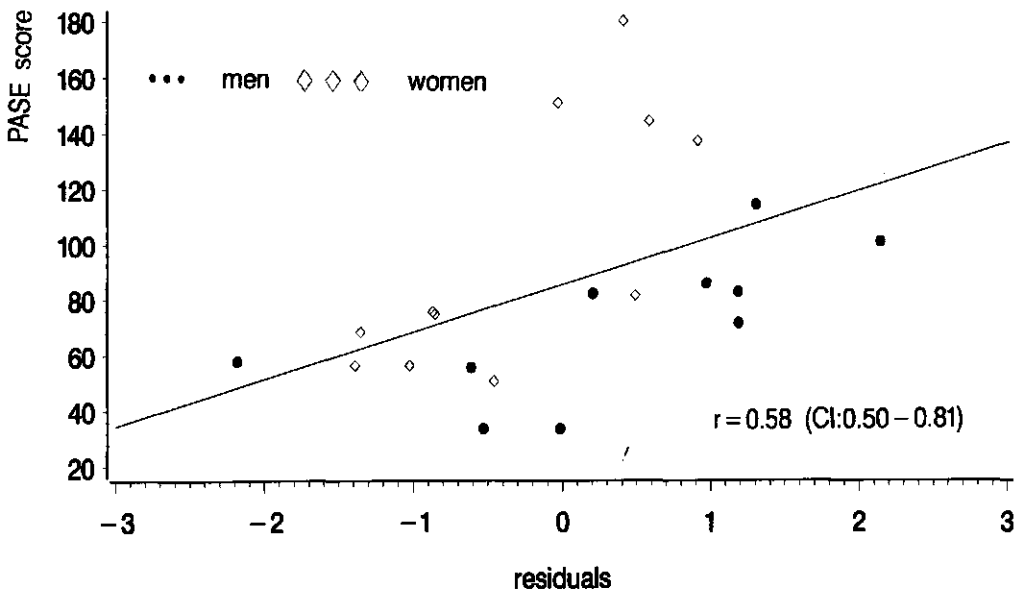
DISCUSSION

The PASE questionnaire is an easily scored, quick tool to assess physical activity in an elderly population. PAR (TEE/RMR) as well as the residuals from the regression analysis with TEE as dependent and RMR as independent were used as measures of physical activity. Both measures were significantly correlated with the PASE score (r = 0.68 and r = 0.58 respectively), indicating that PASE discriminates categories of physical activity reasonably well and therefore is suitable for epidemiological studies. However, PASE does not accurately measure individual metabolic activity.

Energy expenditure

Lately, there has been some discussion on what would be the best way to correct TEE by RMR in order to estimate physical activity[15,16]. Carpenter has suggested the use of residuals of the regression TEE = RMR, rather than the ratio TEE/RMR for comparison of physical activity between subjects, because the regression line of TEE and RMR generally does not pass through the origin. Cole and colleages[15] on the other hand showed that the ratio truly is a valid index of TEE corrected for RMR, using data from a group of 574 adults and children. In our study the intercept was significantly different from zero in both the linear and the log-log model. Consequently, PAR may overestimate physical activity in subjects of our group with a low RMR (women) as compared to subjects with a high RMR (men). We therefore believe that use of the residual method is more appropriate for comparison of physical activity in our study than use of PAR. We still present PAR in this article because it is widely used.

PASE-score

Women of our study population had higher PASE scores than men. The mean difference in PASE-score between men and women was mainly due to a greater engagement of women in heavy housework and taking care of others, which

added respectively 25 and 35 points to the score. However, the RMR-adjusted energy expenditure levels of women, were not higher than men. This may indicate that the PASE questionnaire overestimates womens' physical activity as compared to men, due to an incorrect weighing of heavy housework and caring for others. We therefore conducted an additional analysis in which we assigned successively one half and one quarter of the original item weight to these activities. As expected, the correlation coefficients improved with both measures to 0.68 and 0.71 respectively for one half the item weight and 0.71 and 0.74 for one quarter of the item weight, men and women combined. The difference in mean PASE-score between men and women resulted in a weaker correlation between PASE score and the residuals in the total group as compared to the gender specific correlations.

The stronger correlation between PASE-score and PAR, as compared to the residuals, in the total group can be explained by a concomitant higher PASE-score and higher PAR in women.

Washburn et al report higher PASE-scores for men than women in both younger and older elderly[8]. The difference with our study group may be explained by a more equal division of heavy housework and taking care of others among American men and women, or by a greater engagement of American men in gardening, which is designated to a score comparable to heavy housework. The paper reports a higher engagement of American elderly in lawn work (45.6% vs 9.5%) and outdoor gardening (26.8% vs 4.8%) as compared to our population and although no gender specific data are presented, it is likely that men more frequently perform gardening activities than women. Our study was carried out in the winter period during which hardly any garden work is performed.

Compared to the American elderly, the elderly in our population spent more time on walking (and bicycling) per day (1.10 hr vs 0.65 hr) and on strenuous sport activity (0.19 hr vs 0.07 hr), the latter partly due to the intervention programme. Strenuous activity does not highly contribute to the PASE-score (an hour of heavy sport activity per week for example results only in 3.3 extra points), but this seems justified, because in our study group it also did not significantly affect total energy expenditure. Taking item weights two or three times higher for heavy sport activity did not produce higher correlation

coefficients. It might be argued that the physical activity of the intervention was not sufficiently represented in the PASE score of the intervention subjects. However, total energy expenditure on physical activity was not different between intervention and control subjects (PAR: both groups 1.82, residuals intervention 0.14, control -0.15). Thus, it seems that the intervention programme did not disturb the performance of the PASE.

Conclusion

The PASE questionnaire proved to be a reasonably valid method to classify healthy elderly people into levels of physical activity. We do believe however, that if time spent on gardening, housework and taking care of others, were taken into account in calculation of the score (similar to calculation of sport and recreational activities) or if the item weights of these activities would be reduced, classification would be even better. This might also prevent overvaluation of gender specific tasks, such as housework and gardening. Although the PASE score does not reflect actual metabolic activity, it may be very useful for characterising physical activity level in large epidemiological studies. However, because some highly contributing activities may be different between populations (i.e. outdoor activities can only be performed under good weather conditions, or distribution of household tasks), one should also be cautious in comparing PASE scores among populations with different background.

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CHAPTER 8

Short note on (long-term) adherence to physical training; Comparison between two exercise protocols

Introduction

Until now most studies investigating the relation between exercise and health in elderly have focussed on physiological effects. Information about the feasibility and continuity of regular exercise in this age group is sparse. For example, little is known about motives of elderly to exercise and how exercise training is experienced. 'Do they enjoy it; are they motivated?' and even more important, 'Do they continue with physical activity, once the intervention programme is over?' Therefore, all subjects of the intervention group were followed up for 6 additional months, in order to monitor their physical activities. In this chapter we will briefly discuss the two different intervention programmes in terms of adherence and continuation of regular exercise.

Adherence to the intervention protocols

Bicycle group: Adherence to the bicycle programme was determined as a proportion of 3 targets: (a) intensity, (b) days per week and (c) duration per training session. The adherence among subjects who stayed in the programme until the end was impressive; 98%, 84% and 89% respectively, considering the intensity and duration of the cycling programme. Main reasons for non-adherence were illness and vacation.

Still, not everyone was able to complete the 6 months' bicycling programme. In fact, drop out was 32%, half of which was due to lack of motivation. Moreover, although we can not quantify it, some of the participants continued with the programme, because they were determined to 'finish what they started', and not because they still enjoyed it. Thus, regular intensive training on an exercise bike at home is not feasible for all elderly people.

All-round activity group: Attendance to the programme in the all-round activity group was monitored by the instructor. For men and women this was 72% and 81% respectively. Considering the fact that the hours were fixed, we believe that this adherence was again very good. Non-adherence to the programme in the all-round activity group was, like in the bicycle group, also mainly due to

illness and vacation. Lack of motivation played a minor role. Drop out (23%) was mainly due to an overbooked agenda.

The training programme was evaluated after the intervention period. 36% of the elderly answered that 3 times per week training was too often, while 64% thought it was good. The intensity of the training was good for 79% of the elderly, 9% considered it too high and 12% too low. Ball games were preferred by 64% of the elderly group, physical conditioning by 21% and jogging by 6%. All participants were convinced that the training session enriched their lives, both physically as well as mentally. Especially the social interaction with men and women of their age was greatly appreciated. This also became apparent when, after the intervention period, almost 90% of the subjects continued with the training sessions on their own initiative and expense.

Longterm adherence of regular physical activity

In order to evaluate post-intervention exercise, men and women of the intervention group were invited for a personal interview about their habitual activities, 6 months after they left the programme. In total 46 men and 34 women participated, 84% and 76% of the invited subjects.

Bicycle group: Six months after the intervention programme, elderly men and women of the bicycle group reduced time spent on sport activity[1] (with 40% and 80% respectively). Women became even less active in sport than before the intervention period (now only about 2 hours per months). However, remarkably, mean hours of outdoor bicycling were doubled in women (from 95 to 185 minutes per week) and also slightly increased in men (from 130 to 145 minutes per week). Hours spent on walking did not materially change.

All-round activity group: Subjects in the all-round activity group also reduced time spent on sport activity. Instead of 20 hours per month, men spent about 11 hours per month on sport activity. In women these numbers were 15 and 8 hours respectively. Most elderly subjects continued with the all-round training sessions, but only once per week for 1.5 hour (instead of 3 times an hour). Mean hours spent on walking per week did not markedly change, but mean

hours spent on outdoor bicycling was reduced with about 45% (from 130 to 90 minutes per week).

Summary and conclusions

In summary, participants of the intervention groups who completed the protocol adhered very well to the programme. It may, however, overestimate adherence to exercise programmes in the general elderly population, because our participants were not only relatively healthy and active, but also very motivated. The high drop out in the bicycle group, due to lack of motivation, suggests that individual activity is less stimulating than groupwise physical activity. Six months after the intervention, subjects had about halved the time spent on exercise. Therefore, a training programme, such as the one described in this thesis does not seem feasible in the long term. Since group training has more chances of success in elderly people, it should preferably be recommended to all elderly individuals.

[1] Sport activity comprised tennis, swimming, bal-games, horse-back-riding, gymnastics and exercise biking.

CHAPTER 9

General Discussion

The main objective of the study presented in this thesis was to investigate the effect of regular physical activity for 6 months, either individually on an exercise bicycle or group-wise in a supervised all-round exercise programme, on classical and on some more recently emerged CHD risk factors ('new risk factors') in a healthy elderly population. The classical risk factors have been addressed in Chapter 2, and the new risk factors, such as fibrinogen, factors involved in the fibrinolysis and autonomic regulation of the heart have been reported in Chapter 3 to 5. The focus of the thesis is on the effects of training on the new risk factors, because firstly, there is a great paucity of information on this association and secondly, these new risk factors may be particularly important in elderly. In general, advanced atherosclerosis is prevalent in elderly people, and coagulation factors like fibrinogen, and fibrinolytic factors are specifically associated with the progression of atherosclerosis and manifestation of thrombosis. Unfavourable autonomic control may add to the risk of myocardial infarction and may trigger cardiac arrhythmia. In addition to risk factors for CHD, we also investigated the effect of regular activity on physical and psychological well-being.

In this chapter we will start with briefly summarising the most important results of the study and compare them with those of other studies. Blood pressure, a risk factor that has not been described in this thesis, will be addressed as well. Then, the biological inference of our results will be discussed. Furthermore, we discuss some problems which are specifically encountered in intervention studies in the elderly population[1] and address the internal and external validity and power of the study. The chapter closes with the possible health impact of the training effects observed in our study, a general conclusion and suggestions for future research.

Main findings

Physical Fitness. After 6 months of training, elderly subjects of both intervention groups had significantly improved physical fitness and strength. Both maximal oxygen consumption and maximal exercise capacity gained about

9% (*Chapter 2-5*). Previous studies by others, showed stronger increases,[2,3] but since initial fitness levels of our participating elderly people were relatively high, we believe that 9% increase is still considerable. It indicates that at older age, fitness can be improved and that the intervention was successfully applied.

Classical risk factors. Men and women of the intervention group showed a favourable shift in most of the conventional risk factors (**Table 1.1**). However, only the reduction in serum triglyceride concentration in women was significantly different from the change in controls. The beneficial shift in HDL (*Chapter 2*), coincided with similar changes in the control group and could therefore not be attributed to the programme as such. No effect was observed on total serum cholesterol or LDL. Our results are in line with findings from earlier endurance exercise training studies in older men and women, which generally report increase in HDL, reduction in triglyceride concentration and unchanged total serum cholesterol and LDL concentration.[4-6]

As depicted in **Table 1.1**, reduction of blood pressure was similar in the intervention and control groups, and no training effect could be inferred. This is in disagreement with earlier studies performed in elderly, which showed a fall in blood pressure after regular training, even when intensity was moderate or low. However, unlike our study, these studies were mainly performed in hypertensives,[7,8] who may be more susceptible to the effect of training. Also, contrary to earlier reports in elderly, no effect was found on fasting insulin. However, the reduction in insulin concentration after training may be a consequence of training-induced changes in body composition,[9] which could not be demonstrated in our group of elderly people.

New risk factors. t-PA activity was significantly increased in subjects of the bicycle group (11%, *Chapter 3*). t-PA facilitates the conversion of plasminogen into plasmin, which degrades fibrin clots and removes fibrin from the vascular wall. Also PAI-1 antigen concentration, the rapid inhibitor of t-PA, decreased although not statistically significant. This beneficial shift in fibrinolytic factors was accompanied by an unexpected moderate increase in fibrinogen concentration of 6% in subjects of the intervention group. Since the background of the increase in fibrinogen is unclear, we do not know if, or to

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what extent, the increase in fibrinogen may counteract the possible benefits of the fibrinolytic factors. Only one study has reported effects of training on fibrinolysis and fibrinogen in elderly people, but unfortunately this study lacked a control group.[10] Studies in middle-aged people until now are inconsistent, and report either beneficial or no effects, on fibrinolysis as well as fibrinogen.[11-14]

Table 1.1. *Percentage change of risk factors as compared to baseline levels, among subjects in the intervention groups (combined) and control group.*

risk factor	WOMEN intervention	control	MEN intervention	control	TOTAL intervention	control
conventional						
Total cholesterol	↓	0	↓	0	↓	0
HDL	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑
Triglycerides	↓↓ *	↑	↓↓	0	↓↓	↑
Diastolic BP	↓	↓↓	↓↓	↓	↓	↓
Insulin	0	↑↑	↑↑	↓	↑	↑
new						
t-PA	↑↑	↓↓	↑↑↑ *	↓	↑↑↑ *	↓
PAI-1	↓	↑↑	↓	↓	↓	↑
Fibrinogen	↑↑	↑	↑↑ *	↓↓	↑↑ *	↓
HRV: SD-RR	↑↑↑	↓	↑	↓↓	↑↑ *	↓↓
LF	↑↑↑↑	↓↓	↑	↓↓↓↓	↑↑↑ *	↓↓↓
QT interval	↓*	0	0	0	↓ *	0

↑: increase 1< 5%, ↑↑: 5<10%, ↑↑↑: 10<15%, ↑↑↑↑: >15%, 0: -1 < >1%, opposite arrows indicate similar percentage of decrease. HRV:heart rate variability during the day, SD-RR: standard deviation of RR interval, LF: low frequency component (0.05-0.15 Hz). * p<0.05, difference with change in the control group

In addition, elderly subjects of the intervention group increased heart rate variability during the day (HRV) (*Chapter 5*) and reduced heart rate adjusted QT interval (*Chapter 4*). Both changes probably represent increase in para-sympathetic activity and a more favourable autonomic balance. Training may

counteract the unfavourable shift towards sympathetic activity with advancing age, and may improve the autonomic control of the heart. This may prevent arrhythmia and sudden death. To our knowledge only one study has investigated the effect of training on HRV in elderly people,[15] and also observed a beneficial change. No reports on training effects on QT interval have been found in the literature.

Physical and psychological well being. Physical self-efficacy, in general, and perceived fitness, walking pace, flexibility, speed of response and strength, in specific, were improved in the subjects of the intervention groups, as compared to the controls. Our results are in line with previous studies reporting the effect of training on physical self-efficacy.[16,17] Symptoms of depression were slightly reduced in subjects of the intervention groups, but not statistically significant as compared to the change in the controls (*Chapter 6*). A reduction in depressive symptoms has been reported before,[18-20] however, other studies did not find any training effect.[21,22]

(Long-term) adherence: Adherence to the bicycle and all-round exercise protocols was satisfactory among the subjects who completed the study until the end. Non-adherence in this group was mainly due to illness and vacation. However, a considerable proportion of the elderly could not comply with the programmes and dropped out during the intervention (32% bicycle group, 23% all-round activity group, lack of motivation and lack of time being the main reasons respectively). These data suggest that group-wise training consisting of an all-round exercise programme is more stimulating for elderly and therefore preferably recommended over individual training. Six months after the intervention, subjects had about halved the time spent on exercise. Therefore, a training programme, such as the one described in this thesis does not seem feasible (without additional effort) in the long term (*Chapter 8*).

Validity of physical activity questionnaire. The modified 'Physical Activity Scale for Elderly' (PASE) proved to be a reasonably valid method to classify the healthy elderly people participating in our study in categories of physical activity. Validity was assessed using energy expenditure assessed with the

doubly labelled water method as the standard. The PASE proved to be a very useful tool to monitor physical activity regularly over a period of time. It may be especially useful in large epidemiological studies, since it is easily and quickly administered (*Chapter 7*).

Biological inference

Atherosclerosis is caused by multiple interacting factors, such as high blood pressure, disturbed lipid metabolism, endothelial cell damage leading to platelet aggregation, and disorders of the fibrin balance leading to persisting fibrin deposition. A disturbed fibrin balance at the vessel wall may be due to either increased fibrin formation or impaired fibrinolysis. Plasma fibrinogen affects the formation of fibrin thrombi[23] and is an important determinant of platelet aggregation.[24] Impaired fibrinolysis may predispose to fibrin deposits and contribute to (a) the pathogenesis of atherosclerosis and to (b) occlusive thrombus formation on plaques provoking atherothrombosis. The latter is the most common precipitating event causing of acute myocardial infarction.[25]

Epidemiological data strongly suggest that insulin resistance, associated with abdominal adiposity, is involved in the pathogenesis of atherothrombosis.[26] It has been suggested that hyperinsulinemia promotes atherosclerosis by a direct effect of insulin on the vascular wall (although likely to be modest[27]), or (more important) by an effect on cardiovascular risk factors, such as dyslipidemia (increased VLDL, decreased HDL)[28,29] and hypertension. Recently, it was suggested that PAI-1 is also related to insulin resistance. In vitro studies showed that insulin stimulates PAI-1 secretion by cultured human hepatocytes.[30] Finally, insulin resistance has been linked to excessive activation of the sympathetic nervous system.

It may be speculated that training has a beneficial influence on insulin resistance by favourably changing body composition. Reduction of body fat, may result in reduced insulin resistance and insulin concentration. Reduction in insulin concentration may subsequently lead to beneficial changes in

triglycerides, lipoproteins and possibly PAI-1, sympathetic activity and fibrinogen (see **Figure 9.1**).

Figure 9.1 *Possible biological mechanism, through which physical activity may relate to coronary heart disease.*
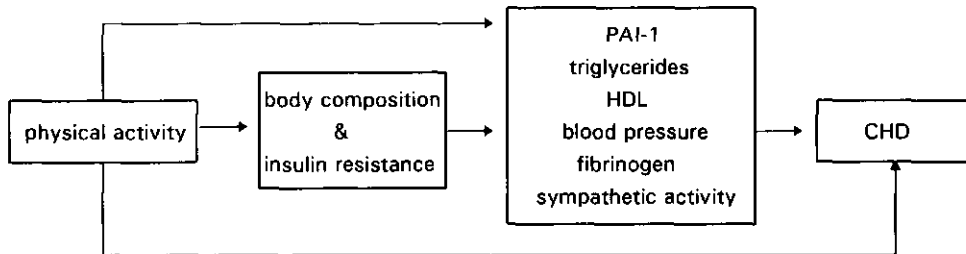
In our study we have correlated the new risk factors with characteristics of the so-called 'insulin resistance syndrome' (IRS), namely serum HDL-cholesterol, serum triglycerides and insulin concentration, body weight and blood pressure, with respect to baseline levels, and changes during the intervention. As described in Chapter 3, PAI-1 antigen concentration, both baseline and change, were associated with fasting insulin and triglyceride concentration, body weight and HDL. Fibrinogen was related to HDL, but t-PA activity was only at baseline related to body mass index, HDL and blood pressure. Increase in HRV was also associated with a reduction in body weight ($p = 0.03$), but not with change in any other IRS characteristic. No indications were found for a possible mediating role of insulin resistance in the association between physical training and QT_c, although at baseline QT_c was linked to body mass index, triglyceride, HDL and fasting insulin concentration (Chapter 4). Associations were generally stronger in women. This may partly be explained by the fact that men, who survive till older age, are less sensitive for insulin than women of the same age,[27] due to insulin-androgen interaction[31].

Therefore, although we could not demonstrate a mean reduction in body weight and fasting insulin in subjects of the intervention group, changes in new

risk factors were often related to changes in weight and fasting insulin. Notice that the absence of body weight reduction does not exclude the possibility that subjects changed their body composition, by losing fat mass and gaining muscle mass. Moreover, we did not measure insulin resistance itself, but used fasting insulin as a proxy. Therefore, we can not rule out the possibility that change in insulin resistance among subjects of the intervention groups has occurred.

In conclusion, our data can not provide evidence that exercise induced change in the new risk factors is mediated by change in insulin resistance, but do give an indication that PAI-1 reduction may be affected by this.

Methodological considerations

A major advantage of a randomised controlled intervention study is that, on average, the intervention and control group are expected to be comparable with respect to study parameters and confounders, even unknown confounders. Potential confounding, caused by differences in baseline characteristics that affect the change over the intervention period, is hereby reduced. Since, also the probability of possible differential errors is smaller than in observational studies, experimental studies provide the strongest evidence for causality.

Still, physical activity intervention has some drawbacks, compared with many clinical or pharmacological trials, since it cannot be properly placebo-controlled, nor blinded. This may affect the internal validity of such a study. On top of that, studies in the elderly are beset by many difficulties, that are less a problem in studies of younger people. For example, willingness to participate and adherence are lower in elderly than in younger groups, due to physical incapacity, or family circumstances[1]. This may affect both external and internal validity of the study. In the following the internal and external validity as well as the power of the study will be addressed.

Internal validity

Success of randomisation: Despite randomisation, men and women of the all-round activity group were somewhat younger and had a higher body mass index than the elderly subjects of the bicycle and control group. This may suggest that randomisation was not completely successful in achieving the desired comparability of the groups. However, it is not conceivable that these differences will have had a strong modifying effect on the changes in risk factors as a consequence of training, and will have biased the results to a great extent.

Selection bias: As referred to in the previous chapters, premature withdrawal from the intervention study was highest in the intervention groups (32% in the bicycle group and 23% in the all-round activity group versus 5% in the control group). Drop out, as observed in our study, is inevitable and an inherent problem in an intervention study with physical activity, especially when elderly people are involved. However, if reasons for drop out during the intervention were related to the change in the study parameters, selection bias may have been introduced. Indeed, in our study reasons for premature withdrawal were different between the intervention and control group. In the all-round activity group it was mainly due to time constraints, and in the bicycle group it was mainly due to motivation problems and physical restraints, whereas in the control group it was mainly due to family circumstances (Chapter 2). Because we did not perform a post intervention measurement among subjects who withdrew prematurely, we could not investigate the effects of training in these subjects. However, since in general, drop outs were less fit than compliers, and the greatest changes in risk factors may be expected in the least fit, we believe that a possible selective drop out may have rather led to an underestimation than an overestimation of the training effect.

Observation bias: Because our study was not completely blinded, we can not rule out the possibility of observation bias in our study. However, observation bias is likely to be limited to only a few study parameters in the post intervention measurement; All baseline measurements were done before the

randomisation and except for the interview, Anthropometry and blood pressure measurement, post-intervention data collection was blinded for the subjects' assignment. Anthropometry and blood pressure measurement were performed according to strict protocols and the interview consisted of mainly prestructured answer categories. Therefore, risk of interviewer bias was minimised. Nevertheless, the subjects in the intervention and control group may have reported events differently.

In addition, inaccuracies in laboratory measurements of the blood parameters may have occurred. However, since such inaccuracy is expected to be similar in intervention and control group and therefore non-differential, it will most probably have led to an underestimation of the true differences in effect between intervention and control group.

Change in the control group: As reported in Chapter 2 to 5, CHD risk factors were also changed in subjects in the control group, in either a beneficial direction, (e.g. HDL and blood pressure), or an unfavourable direction (e.g. HRV, t-PA and PAI-1). Theoretically, improvement in risk factors might be explained by an increase in physical activity similar to that in the intervention group. However, if this were the case, one would expect to find an improvement in all parameters. The reduction in blood pressure at the post intervention measurements in both groups may be explained by the fact that subjects were then more at ease, than at the pre-intervention measurement.

In addition, seasonal variation in the parameters may explain the change in the control group (and intervention group). However, information on seasonal variation in the new risk factors is sparse, and precludes speculations on its potential impact.

Confounding: During the intervention, change in unmeasured parameters, independently associated with both physical activity and the CHD risk factor, may have confounded the observed associations. It remains unclear to what extent this confounding may have biased our results. However we believe that this bias is probably minor compared with bias introduced by a selective drop out.

External validity

The participants of our study were not a representative sample of a general elderly population in the Netherlands. Not only did we select the elderly on basis of good health (see inclusion criteria introduction, **Figure 1.3**), those willing to participate were more active and considered themselves more healthy in comparison with those who did not. The selective nature of our study population limits the generalizability of our study results to the general elderly population. We do however expect, that were the same intervention performed in the general population with similar adherence, the effect of training would have been similar, if not greater, since health benefits are expected to be highest in the least active groups.[32]

In the 'main findings' and in the discussion sections of the separate chapters we have already addressed the comparability of our findings with those of other studies.

Power of the study

The purpose of the study was to recruit 100 subjects in both bicycle and control group and 50 subjects in the all-round activity group. Unfortunately, these numbers were not met. Not only were more elderly people excluded during the screening phase (30%), also drop out was higher than initially expected. Originally, the numbers per group were based on a power calculation for the classical risk factors (serum lipids and blood pressure), because information on inter- and intra-individual variation for the new risk factors was lacking. Despite smaller numbers we were, fortunately, able to demonstrate significant changes in most of the new risk factors in the intervention as compared to the controls, except for PAI-1. Owing to the large variation in PAI-1 change (standard deviation of change was 35% of initial value), the power of this study was insufficient (only 20%) to observe a difference of 5 ng/mL (10% of baseline) between intervention and control group, with a significance level of 0.05. Training effects on blood pressure, HDL, insulin and total serum

cholesterol were either absent or too small (< 5%) to be demonstrated in this study, at this level of significance.

Public health implications

In industrialised societies the proportion of individuals reaching old age has been increasing and will probably continue to increase in the future. Among the elderly population, vulnerability to most diseases is increased. Diseases of the cardiovascular system cause more than 40% of the deaths in the elderly population, of which CHD is the most common disease. In 1995, more than 80% of the total CHD deaths in the Netherlands were among subjects of 65 years and older.[33]

The aetiology of CHD is multifactorial. Although elderly people are survivors and may therefore be less susceptible to CHD, classical CHD risk factors are still important in people over 65 years of age.[34,35] Also the new risk factors, described in this thesis, are likely to be important predictors of CHD in elderly. The atheroma related morbidity and mortality is mostly due to plaque ulceration followed by thrombosis. An impaired fibrinolysis may contribute to the thrombotic events whereas autonomic balance may predict the outcome of the event.

Considering this, we have solid reason to assume that the observed beneficial effects of training on fibrinolytic activity and autonomic balance, observed in our study, may affect CHD risk. Moreover, the increase in physical fitness, observed in our study, may affect CHD and total mortality risk. Blair *et al.*[36] have reported a four-fold risk of total mortality in men and women of the lowest fitness quintile as compared to the highest, independent from CHD risk factors. The association was even stronger for CHD (eight-fold risk), but the reported relative risk was solely adjusted for age and not for the risk factors of CHD. The increase in fibrinogen, especially observed after strenuous exercise, may warrant safety and may suggest preference of moderate activity.

Altogether, it is very likely that training will beneficially influence CHD risk in elderly subjects. However, the magnitude of the impact remains difficult

to determine. Unfortunately, until now very few studies have addressed the predictive value of fibrinolytic factors, such as PAI-1 and t-PA, or measures of autonomic balance, such as QT_C interval and HRV, on CHD risk in elderly. Therefore we are unable to quantify the public health impact with respect to CHD of our activity programme. However, since elderly people tend to have more atherosclerosis and a more unfavourable autonomic balance than middle aged, the impact in absolute terms may be even greater than in middle-aged subjects.

Finally, but very important, apart from an effect on morbidity and mortality, regular physical activity may also slow down the age-associated loss in functionality and independence. In our study, physical self-efficacy was markedly increased among subjects of the intervention groups. Thus, regular physical activity may facilitate increased self-confidence and competence in dealing with daily activities, like dressing, shopping and washing, and consequently with the quality of life.

Future research

Our study was performed in a rather healthy and active population. There still lies a great challenge in exploring the effects of regular exercise in less active and less healthy elderly, e.g. frail elderly. Intervention among frail or primarily inactive elderly will particularly be difficult in terms of willingness to participate and adherence. Still, insight into training effects in these groups is needed, not only with respect to CHD risk factors, but also to determine training effects on physical functioning and well-being. With this information available, recommendation for training in elderly people in general and specific subgroups can be developed.

In addition, physiological and biochemical research is needed to investigate the mechanisms underlying the observed responses to exercise in elderly, especially with respect to the new risk factors, described in this thesis. Evidence from these type of studies may support inference on the causality of the associations.

Finally, research is warranted to investigate the predictive value of the new risk factors in elderly people. As previously stated in this thesis, we speculate that the new risk factors may be particularly important in elderly. However there is insufficient data to support this hypothesis.

Conclusion

Although definitive evidence documenting the beneficial effects of exercise training on mortality and disability in the elderly is still lacking, it becomes more evident that CHD risk factors and physical fitness and self-efficacy, which are important determinants of the quality and quantity of life for older individuals are beneficially affected by exercise training. We think that regular physical exercise may be recommended to all elderly individuals, provided that it is performed safely. Safety precautions should include (a) a prior medical examination, (b) a balanced training program, in which intensity and frequency are slowly and gradually increased, and, if possible, (c) supervision by an experienced instructor. Exercise in group setting would be preferred, in order to assure long-term adherence.

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Summary

Evidence of an important role of physical activity in the primary prevention of coronary heart disease (CHD) has grown in recent years. Regular physical activity may have a favourable impact on 'classical' risk factors, such as overweight, low serum high density lipoprotein cholesterol (HDL) and high serum low density lipoprotein cholesterol (LDL), high serum total cholesterol, high serum triglyceride concentration and high blood pressure. Lately, also beneficial effects on newly established risk factors, such as fibrinolytic factors (tissue-type plasminogen activator (t-PA) and plasminogen activator 1 (PAI-1)), plasma fibrinogen, and factors reflecting the autonomic regulation of the heart (heart rate variability and QT_c interval), have been suggested.

Until now, most studies investigating the effect of regular physical activity on CHD risk have been performed in middle-aged subjects. Information about training effects on CHD risk factors in elderly is sparse, especially with regard to the 'new' risk factors. Insight into the effect of regular physical activity in elderly people is particularly important, (1) the proportion of inactive people is higher at older age, (2) CHD risk factors become more unfavourable with advancing age and remain important in predicting CHD. Therefore, managing of these risk factors may have an important impact on public health.

We have carried out a randomised controlled intervention study, which addressed the effects of a 6 months training programme on the 'classical' and 'new' risk factors, described above, in a healthy elderly population (60-80 years old). Furthermore, effects on physical and psychological well-being were studied. These elderly (n = 229) were randomly allocated to 3 groups: (1) an exercise bicycle group, in which subjects trained 4 times per week, for 30 minutes, at about 70% of their maximal capacity (Wmax), individually at home, (2) an all-round activity group, in which subjects trained 3 times per week for 45 minutes, performing various activities, such as ball games, callisthenics and exercise to music, and (3) a control group, in which subjects were asked to maintain their habitual activity pattern.

After 6 months training, physical fitness (maximal oxygen consumption (VO_2max) and maximal capacity (Wmax)) was significantly increased in subjects of both training groups with about 9%. This increase was significantly different from the controls ($P < 0.01$).

No significant changes were observed in body weight or body fatness, measured with the sum of skinfolds, in subjects of the training groups. Serum HDL-cholesterol, total serum cholesterol and serum triglycerides changed in a favourable direction, but only triglyceride concentration in women of the training groups was significantly reduced (-0.11 ± 0.06 mmol/L) as compared to the controls ($P < 0.05$), and could be attributed to the intervention programmes *(Chapter 2)*. In addition, we did not observe a significant effect of training on blood pressure or fasting insulin concentration.

In general, elderly people have advanced atherosclerosis and higher risk of thrombosis. Therefore, factors involved in the progression of atherosclerosis and onset of thrombosis (t-PA, PAI-1 and fibrinogen) may be of particular importance in this age-group. After 6 months training (exercise bike), t-PA activity, a measure of fibrinolytic activity, the process that counteracts atherosclerosis and thrombosis, was significantly higher ($+11\%$, $P < 0.05$) compared to the control group. Mean PAI-1 antigen, the inhibitor of t-PA was lower, although not significantly, also suggesting an elevation of fibrinolytic activity. Unexpectedly, we observed a moderate increase in plasma fibrinogen ($+6\%$, $P < 0.05$), a presumed risk factor for CHD. This increase is difficult to interpret. It may reflect an unfavourable inflammatory reaction of the vessel wall to strenuous exercise, or a shift in the balance between coagulation and fibrinolysis. This shift may provide a quicker response to vessel damage, with lower risk of thrombus formation *(Chapter 3)*.

Prolongation of heart rate adjusted QT interval (QT_c), a characteristic of the electrocardiogram, is associated with an increased incidence of CHD mortality. Prolongation is caused by a heterogeneity in the repolarisation of the heart, which may be caused by sympathetic imbalance, particularly in the presence of high sympathetic activity. Mean QT_c and mean resting heart rate changed favourably in men and women of both training groups. However, only in women this change differed significantly from the controls. The beneficial

shift in QT_C may be caused by a more favourable autonomic balance through increased parasympathetic activity *(Chapter 4)*.

Heart rate variability (HRV), a measure of the spontaneous fluctuations around the mean heart rate, is also a tool to investigate the sympathetic and parasympathetic function of the autonomic nervous system. Reduced HRV, possibly reflecting reduced parasympathetic activity, was reported to be associated with a two-to-three-fold risk of total mortality and cardiac events, in apparently healthy subjects. After 6 months training, HRV was significantly increased during the day (+6%, $P < 0.05$), especially among those inactive in sport at the start of the study (+17%, $P < 0.05$). The effects of training on HRV confirm the hypothesis, that, in elderly subjects, physical training can increase parasympathetic activity and can positively modify factors associated with an increased incidence of CHD *(Chapter 5)*.

Apart from CHD risk factors, we also studied the effect of training on physical and psychological well-being. Physical well-being, or self-efficacy, was measured with the LIVAS-scale ('Lichamelijke Vaardigheden Schaal'), a Dutch translation of a sub-scale of the 'Perceived Physical Activity Scale', and psychological well-being with the Center for Epidemiologic Studies Depression-Scale (CES-D). After 6 months, physical self-efficacy was increased in both training groups, as compared to the controls, but particularly in subjects of the all-round activity group ($P < 0.05$). Symptoms of depression were markedly reduced in men and women of the training groups, but not significantly different from the controls. Elevation of physical self-efficacy (LIVAS-score) was significantly associated with a reduction in symptoms of depression (CES-D score). Therefore, we may speculate that increase in physical self-efficacy by physical activity, may ultimately lead to a reduction in occurrence of depressive symptoms in elderly people *(Chapter 6)*.

Adherence to the protocols was satisfactory among the subjects who stayed in the study until the end. In the bicycle group, the rate of adherence to the training frequency was more than 80%. In the all-round activity group, mean attendance was about 75%. The largest drop out took place in the intervention groups (bicycle group 32%, all-round activity group 23%, control group 5%). Most important reason for drop put in the bicycle group and all-

round activity group were lack of motivation, and lack of time respectively. These results suggest that individual activity is less stimulating than group-wise physical activity. Six months after the intervention, subjects had about halved the time spent on exercise. However, most subjects of the all-round activity group had continued with the training programme, but with a lower frequency. Therefore, a training programme, such as the one described in this thesis does not seem feasible in the long term, if not additionally supported. Group training is preferred above individual training, because long-term adherence is likely to be better *(Chapter 8)*.

In addition to studying the effects of regular physical activity, we have also reported on the validity of a physical activity questionnaire, the so-called 'Physical Activity Scale for the Elderly'-questionnaire (PASE). The score derived from the questionnaire was compared with energy expenditure, measured with the doubly labelled water method. The PASE proved to be a reasonably valid method to classify healthy elderly people in categories of physical activity. The PASE is an easily scored and quickly administered questionnaire and may therefore be particularly useful in large epidemiological studies *(Chapter 7)*.

In conclusion, regular physical activity beneficially affects CHD risk factors (particularly newly emerged risk factors), physical fitness and well-being. The positive changes in CHD risk factors and fitness very likely reduce the risk of CHD in elderly people. The magnitude of the benefits remains unclear, since there is little information on the predictive value of the new risk factors in elderly. However, since elderly in general have advanced atherosclerosis, it is conceivable that physical training may be even more important in elderly than in younger age-groups. The positive change in physical self-efficacy may, in addition, contribute to a higher quality of life. Group exercise is preferred above individual exercise, in terms of long-term adherence. Therefore, regular exercise (and particularly group exercise consisting of a varied programme) should be recommended to elderly people, provided that it is performed safely.

Samenvatting

Het belang van regelmatige lichamelijke aktiviteit in de primaire preventie van hart- en vaatziekten wordt de laatste jaren steeds vaker gesuggereerd. Regelmatige lichamelijke inspanning heeft mogelijk een gunstig effect op de zogenaamde 'klassieke' risicofactoren voor coronaire hartziekten (CHZ), zoals overgewicht, serum 'high density lipoprotein' (HDL), serum 'low density lipoprotein' (LDL), serum totaal cholesterolgehalte, triglyceridegehalte en bloeddruk. Onlangs is ook gesuggereerd dat lichamelijke aktiviteit gunstige effecten heeft op de recent ontdekte risicofactoren, zoals fibrinolytische factoren (weefsel plasminogeen activator (t-PA) en plasminogeen activator remmer (PAI-1), plasma fibrinogeen, en factoren die de autonome regulatie van het hart weerspiegelen (zoals variabiliteit van hartfrequentie en QT_c interval).

Tot op heden zijn de meeste studies naar het effect van regelmatige lichamelijke aktiviteit op risicofactoren voor CHZ uitgevoerd bij mensen van middelbare leeftijd. Er is weinig bekend over de effecten van regelmatig bewegen op risicofactoren voor CHZ bij ouderen. Toch is het belangrijk om hier meer inzicht in te krijgen, omdat (1) het percentage inaktieven toeneemt met de leeftijd en (2) de risicofactoren voor CHZ met het ouder worden in ongunstige richting veranderen, terwijl deze grotendeels hun voorspellende waarde behouden. Het positief beïnvloeden van deze risicofactoren, zal daarom een belangrijke bijdrage kunnen leveren aan de volksgezondheid.

In een gerandomiseerde interventiestudie is het effect van een 6 maanden durend bewegingsprogramma, bij ouderen in de leeftijd van 60 tot 80 jaar, onderzocht op zowel de 'klassieke' als de 'nieuwe' risicofactoren voor CHZ. Daarnaast is het effect van bewegen op het fysiek en psychisch welbevinden bestudeerd. De ouderen (n = 229) werden random verdeeld in 3 groepen: (1) een hometrainergroep, waarin de deelnemers thuis, 4 keer per week, gedurende 30 minuten fietsten met een intensiteit die ongeveer gelijk was aan 70% van hun maximaal inspanningsvermogen, (2) een gevarieerd bewegingsprogramma (MBVO), waarin de deelnemers 3 keer per week, gedurende 45 minuten diverse sportaktiviteiten beoefenden, zoals balsport, 'bewegen op muziek' en kracht- en

flexibiliteitsoefeningen, en tot slot (3) een controle groep, waarin de deelnemers werd gevraagd om hun gebruikelijke aktiviteitenpatroon te handhaven.

Na 6 maanden interventie was de fysieke conditie (maximaal zuurstofopnamevermogen en maximale inspanningscapaciteit) van de deelnemers in de interventiegroepen, significant verbeterd (+9%, $P<0.05$) ten opzichte van de controlegroep. Het lichaamsgewicht en percentage lichaamsvet (gemeten met som van de huidplooien) bleef onveranderd in alle groepen. Serum HDL, totaal cholesterol en triglyceriden waren in een gunstige richting veranderd bij de deelnemers in de interventiegroepen, echter alleen de daling in triglyceriden bij vrouwen (-0.1 ±0.06 mmol/L) was significant ten opzichte van de controlegroep ($P<0.05$). Er is geen effect van regelmatige lichamelijke aktiviteit op de bloeddruk en op het nuchter insuline gehalte waargenomen *(Hoofdstuk 2)*.

Over het algemeen hebben oudere mensen meer atherosclerose (aderverkalking) en een hoger risico op trombose (bloedstolselvorming in het bloedvat). Daarom zijn factoren die betrokken zijn bij de progressie van atherosclerose en het ontstaan van trombose (t-PA, PAI-1 en fibrinogeen) bij ouderen mogelijk extra belangrijk. Na 6 maanden training was t-PA aktiviteit, een factor die de fibrinolyse stimuleert, significant gestegen (+11%, $P<0.05$). Deze verandering was significant in vergelijking met de controlegroep. Ook PAI-1 antigen, de remmer van t-PA was lager, maar dit verschil was niet significant ten opzichte van de verandering in de controlegroep. Onverwacht was de stijging in plasma fibrinogeen, een mogelijke risicofactor voor HVZ, bij de deelnemers in de interventiegroep (+6%, $P<0.05$). Mogelijk weerspiegelt deze stijging een ontstekingsreaktie van de vaatwand als gevolg van zware inspanning. Ook is het mogelijk dat er een verschuiving is opgetreden in de balans tussen stolling en fibrinolyse, welke een snellere respons op vaatwandbeschadiging mogelijk maakt *(Hoofdstuk 3)*.

Een verlengd (voor hartfrequentie gecorrigeerd) QT interval (QT_c) in het electrocardiogram is geassocieerd met een verhoogde incidentie van CHZ. De verlenging is het gevolg van heterogeniteit in de repolarisatie van het hart, wat mogelijk veroorzaakt wordt door een autonome dysbalans, met name wanneer de sympathische aktiviteit hoog is. Na 6 maanden training was het QT_c interval verkort en de rusthartfrequentie gedaald. Echter alleen bij de vrouwen was dit

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verschil significant ten opzichte van de controle groep. Deze gunstige verandering werd mogelijk veroorzaakt door een gunstigere autonome balans, als gevolg van een verhoogde parasympathische aktiviteit *(Hoofdstuk 4)*.

Hartrimevariabiliteit (HRV), is een maat voor de spontane schommelingen rondom de gemiddelde hartfrequentie. Deze maat wordt gebruikt om de sympathische en parasympatische funktie van het autonome zenuwstelsel te bestuderen. Uit eerder onderzoek is gebleken dat een verlaagd HRV, bij ogenschijnlijk gezonde mensen samenhangt met een 2 to 3 keer zo hoog risico op totale sterfte en het krijgen van hartziekten. Uit onze interventiestudie bleek dat, na 6 maanden training, HRV gedurende de dag, significant was gestegen (+6%, $P<0.05$). Het effect van de training was het meest uitgesproken bij de ouderen die voorheen niet aan sport deden (+17%, $P<0.05$). Deze verandering in HRV bevestigt de hypothese dat regelmatige lichamelijke aktiviteit de parasympathische aktiviteit kan verhogen en het risico op CHZ bij ouderen gunstig kan beïnvloeden *(Hoofdstuk 5)*.

Naast het effect op de risicofactoren voor CHZ, is in deze studie ook het effect van bewegen op het fysieke en psychisch welbevinden onderzocht. De lichamelijke vaardigheden werden geschat met behulp van de 'Lichamelijke Vaardigheden Schaal' (LIVAS) , en het psychisch welbevinden met de vertaalde versie van de 'Center for Epidemiologic Studies Depression Scale' (CES-D). Na 6 maanden training waren de lichamelijke vaardigheden bij de deelnemers in de interventiegroepen significant verbeterd ($P<0.05$), met name bij het gevarieerde bewegingsprogramma. Symptomen van depressie waren duidelijk lager na de interventie, bij de deelnemers in de interventiegroepen, maar dit was niet significant verschillend van de controlegroep. Aangezien een vermindering in depressieve symptomen significant gerelateerd was aan een verbetering van lichamelijke vaardigheden, kan worden verondersteld dat een verbetering van lichamelijke vaardigheden uiteindelijk zal leiden tot een vermindering in depressieve symptomen *(Hoofdstuk 6)*.

De deelnemers die de 6 maanden durende interventie hebben volbracht, hielden zich goed aan het trainingsprogramma. In de hometrainergroep werd meer dan 80% van de trainingsessies gevolgd, terwijl de gemiddelde deelname aan het gevarieerde bewegingsprogramma ongeveer 75% was. Echter, het

aantal personen dat voortijdig met de deelname aan het onderzoek was gestopt, was het hoogst in de interventiegroepen (hometrainer- groep 32%, gevarieerd bewegings-programma 23%, controlegroep 5%). De voornaamste redenen van voortijdig stoppen waren motivatiegebrek (in de hometrainergroep) en tijdgebrek (gevarieerd bewegingsprogramma). uit deze resultaten zou geconcludeerd kunnen worden dat individuele sportbeoefening minder stimulerend is voor ouderen dan sporten in groepsverband. Zes maanden na afloop van de interventie was het aantal uren sport per week ongeveer gehalveerd bij de mensen uit de trainingsgroepen. Wel waren bijna alle deelnemers aan het gevarieerde bewegingsprogramma doorgegaan met de trainingen, echter maar 1 keer per week. Blijkbaar is het bewegingsprogramma zoals beschreven in deze studie niet haalbaar op de lange termijn. Groepstraining lijkt, in ieder geval bij ouderen, de voorkeur te hebben boven individuele sportbeoefening *(Hoofdstuk 8)*.

In deze studie hebben we ook een lichamelijke aktiviteiten-vragenlijst, de zogenaamde 'Physical Activity Scale for the Elderly (PASE)' gevalideerd. De score die berekend werd uit de verschillende vragen van deze lijst werd vergeleken met het energiegebruik dat gemeten werd met de tweevoudig gemerkt water methode. De PASE bleek een voldoende valide vragenlijst te zijn voor het indelen van gezonde ouderen in categorieën van lichamelijke aktiviteit. Aangezien de PASE snel en makkelijk is in het gebruik, biedt het een uitstekende mogelijkheid om, met name in grote epidemiologische studies bij ouderen, lichamelijke aktiviteit te meten *(Hoofdstuk 7)*.

Concluderend: Regelmatige lichamelijke aktiviteit heeft een gunstige invloed op een aantal risicofactoren voor CHZ (met name de recent ontdekte risicofactoren), de lichamelijke conditie en het welbevinden van ouderen. De gunstige effecten op de CHZ risicofactoren en de fysieke conditie zullen waarschijnlijk het risico op CHZ verlagen. Echter, de mate waarin blijft nog onduidelijk, aangezien de voorspellende waarde van veel van de besproken risicofactoren bij ouderen, nog verder onderzocht moet worden. Echter, aangezien ouderen in het algemeen meer atherosclerose hebben dan jongeren, is

regelmatige lichamelijke aktiviteit bij ouderen minstens even belangrijk als bij mensen van middelbare leeftijd. Bovendien zal de verbetering in lichamelijke vaardigheden bij hen bijdragen aan een verhoogde kwaliteit van leven. Bewegen in groepsverband heeft bij ouderen de voorkeur boven individuele sportbeoefening. Regelmatige lichamelijke aktiviteit zou daarom meer gestimuleerd moeten worden bij ouderen (vooral groepssport bestaande uit een gevarieerd programma).

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Curriculum Vitae

Albertine Jeannette (Jantine) Schuit was born in Nijkerk, The Netherlands, on November 26th, 1964. In 1982 she completed secondary school (Farel College, Amersfoort). From 1983 to 1987 she studied Consumer Affairs at Hogeschool Diedenoort in Wageningen. After graduating she continued her studies in Household and Consumers Science at Wageningen Agricultural University. Her majors were in Epidemiology and Public Health Care. Furthermore, she investigated the use of primary health care, and the health consequences of garbage disposal in a slum area of Manila, The Philippines. She graduated in September 1990.

From February 1991 until June 1992 she was appointed as a teaching and research associate at the Department of Epidemiology and Public Health, Wageningen Agricultural University. At the same department, in July 1992, she started the Ph.D.-project described in this thesis. In the summer of 1992, she attended the Annual New England Epidemiology Summer Program at Tufts University in Boston, U.S.A. She was registered as Master of Science in Epidemiology in 1993 by the Netherlands Epidemiological Society. In 1994, she visited The Robert Koch Institute, Federal Institute for infectious and non-communicable diseases, Berlin, Germany, for several weeks. In 1995, she worked for several months as a research fellow at the Pennsylvania State University, at the Noll Physiological Research Center and the Center for Special Population and Health, University Park, U.S.A. She was a member of the Education Committee of the graduate school Food Technology, Agro-biotechnology, Nutrition and Health Science (VLAG).

In June 1997, she will start working at the Department of Chronic Diseases and Environmental Epidemiology of the National Institute of Public Health and the Environment, Bilthoven, The Netherlands, as a researcher in the field of physical activity and health.