**Unit for Sports and Exercise Medicine
Institute of Clinical Medicine
and
Department of Public Health**

**University of Helsinki
Finland**

PHYSICAL ACTIVITY, INHERITED CHARACTERISTICS, AND HYPERTENSION

Miika Hernelahti

Academic Dissertation

To be presented, with the permission of
the Faculty of Medicine, University of Helsinki,
for public examination in Auditorium XV,
University Main Building, Unioninkatu 34, Helsinki,
on 5 November, 2004, at 12 noon

Supervisors

Professor Urho Kujala, MD, PhD
Department of Health Sciences
Faculty of Sport and Health Sciences
University of Jyväskylä
Finland

Professor Jaakko Kaprio, MD, PhD
Department of Public Health
University of Helsinki
Finland

Reviewers

Professor Timo Lakka, MD, PhD
Department of Physiology
University of Kuopio
Finland

Docent Timo Kuusi, MD, PhD
Department of Medicine
University of Helsinki
Finland

Opponent

Docent Katriina Kukkonen-Harjula, MD, PhD
UKK Institute for Health Promotion Research
Tampere
Finland

TIIVISTELMÄ

Liikunta on yhteydessä matalaan verenpaineeseen. Perinnöllinen alttius vaikuttaa sekä verenpaineeseen että liikunta-aktiivisuuteen merkittävissä määrin, joten tämä yhteys saattaa osin selittyä geneettisellä valikoitumisella, ts. ne joiden on luontaista liikkua omaavat myös matalat verenpainetasot. Geneettisen valikoitumisen osuutta on vaikea arvioida perinteisissä epidemiologissa tutkimuksissa. Tämän tutkimuksen tavoitteena oli tutkia vapaa-ajan liikunnan ja kohonneen verenpaineen ilmaantuvuuden välisen yhteyden luonnetta.

Liikunnan ja kohonneen verenpaineen ilmaantuvuuden välistä yhteyttä tutkittiin kyselypohjaisin seurantatutkimuksin kolmessa eri kohortissa. Miespuolisia keski-ikäisiä ja vanhempia suunnistajia ja verrokkeja (n=652) seurattiin 11 vuoden ajan sekä miespuolisia entisiä huippu-urheilijoita ja verrokkeja (n=888) 10 vuoden ajan. Suomen Kaksoskohortissa (n=8312) kartoitettiin liikuntatottumuksia kahdesti kuuden vuoden välein vuosina 1975 ja 1981 ja sen jälkeen tutkittiin 9 vuoden seurannassa (vuoteen 1990) kohonneen verenpaineen ilmaantumista.

Geneettisten tekijöiden vaikutusta liikunnan ja verenpaineen yhteyteen tutkittiin kaksoskohortin alaryhmässä (n=350), jossa haastateltiin identtisten ja epäidenttisten kaksosparien elinikäinen liikunta-aktiivisuus ja mitattiin heidän verenpaineensa. Geneettisellä mallinnuksella arvioitiin ulkoisten tekijöiden ja geneettisten tekijöiden osuutta systolisen ja diastolisen verenpaineen vaihtelun selittäjinä. Lopuksi tutkittiin yhtä pääosin perinnöllistä tekijää, lihassolutyyppijakaumaa, verenpainetasojen ennustajana 19 vuoden seurantatutkimuksessa 64 miehen otoksessa.

Verrattuna verrokkeihin veteraanisuunnistajilla ja entisillä kestävyysominaisuuksia edellyttävien lajien huippu-urheilijoilla oli alhainen kohonneen verenpaineen riski (ikävakioitu riskisuhde 0.26 veteraanisuunnistajilla ja 0.67 entisillä huippu-urheilijoilla). Kaksoskohortissa miehillä sekä jatkuva intensiivisen liikunnan harrastaminen että aiempi harrastaminen joka sittemmin on loppunut olivat itsenäisesti yhteydessä alhaiseen kohonneen verenpaineen riskiin (riskisuhteet 0.62-0.69 verrattuna niihin, jotka eivät missään vaiheessa harrastaneet intensiivistä liikuntaa), mikä kertoo että liikunta todennäköisesti madaltaa riskiä kohonneeseen verenpaineeseen, mutta saattaa viitata myös valikoitumiseen. Naisilla liikunta-aktiivisuus ei ollut yhteydessä kohonneen verenpaineen riskiin. Tämä löydös saattaa johtua naisten ja miesten erilaisista liikuntatottumuksista.

Kaksoskohortin alaryhmässä nuoruuden (12-20 vuoden iässä harrastettu) aerobinen liikunta oli yhteydessä matalaan diastoliseen verenpaineeseen ja näiden kahden tekijän geneettiset taustat olivat osittain samat. Viimeaikainen liikunta ei ollut johdonmukaisesti yhteydessä matalaan verenpaineeseen, mikä saattaa johtua liikunnan arvioinnin vaikeudesta tai terveydenhuollon piirissä mitatun korkean verenpaineen jälkeen annetuista liikuntaohjeista.

Suuri osuus hitaita, tyyppi I lihassoluja luurankolihaksissa, ominaisuus joka ei juurikaan muutu liikunta-aktiivisuuden muutosten myötä, ennusti itsenäisesti matalia verenpainetasoja ja selitti osan liikunnan ja matalan verenpaineen yhteydestä.

CONTENTS

ABSTRACT

Physical activity is associated with low blood pressure levels and reduced risk for hypertension. Blood pressure levels and engagement in physical activity are, however, both significantly heritable, and thus genetic selection may influence this association. The role of genetic selection is difficult or impossible to assess in traditional population-based epidemiological studies of the association between exposure and outcome. The aim of the present study was to investigate the nature of the association between leisure-time physical activity and occurrence of hypertension.

The association between physical activity and occurrence of hypertension was investigated in three cohorts by questionnaire-based follow-up studies. Middle-aged and older male orienteering runners and controls (n=652) were followed for 11 years, and male former elite athletes and controls (n=888) for 10 years. Physical activity habits in a cohort of male and female twins (n=8 312) were assessed twice 6 years apart, and after a follow-up period of 9 years, occurrence of hypertension.

Genetic effects in the association between physical activity and hypertension were investigated in a male subgroup (n=350) of the large twin cohort, for which the lifetime history of physical activity in monozygotic and dizygotic twin pairs was determined through an interview, along with measurement of blood pressure. Genetic modelling then allowed estimation of genetic and environmental components of variance of systolic and diastolic blood pressure. And finally, a specific inherited factor, muscle fibre-type distribution, was investigated as a predictor of blood pressure levels in a 19-year follow-up study of 64 unrelated men.

Compared with controls, master orienteering runners and former elite athletes in endurance or mixed sports were at low risk for hypertension (age-adjusted odds ratios (OR) 0.26 and 0.67 respectively). In the twin cohort, men, both persistent engagement in vigorous activity and earlier engagement that had ceased 6 years later were independently associated with lower risk for hypertension (ORs 0.69 and 0.62, respectively, compared with persistent non-engagement), which may be an indication of selection processes. In women, physical activity was not associated with risk for hypertension. This finding may be due to differing patterns of exercise between women and men.

In the male subgroup of the twin cohort, aerobic physical activity in adolescence was associated with low diastolic blood pressure; the genetics regarding these two characteristics were correlated. That recent physical activity was not consistently associated with low blood pressure may be due to difficulties in assessing physical activity or may reflect physicians' recommendations to exercise following high blood pressure readings.

A high proportion of type I (slow-twitch) muscle fibres in skeletal muscle, a characteristic resistant to change along with alterations in aerobic physical activity, was a strong independent predictor of low blood pressure levels, and explained part of the association between physical activity and low blood pressure.

In sum, in men, physical activity is associated with low risk for hypertension. Genetic factors such as muscle fibre-type distribution may explain part of this association.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications; referred to in the text by their Roman numerals, I to V:

I   Hernelahti M, Kujala UM, Kaprio J, Karjalainen J, Sarna S. Hypertension in master endurance athletes. J Hypertens 1998; 16: 1573-1577.

II   Hernelahti M, Kujala UM, Kaprio J, Sarna S. Long-term vigorous training in young adulthood and later physical activity as predictors of hypertension in middle-aged and older men. Int J Sports Med 2002; 23: 178-182.

III   Hernelahti M, Kujala UM, Kaprio J. Stability and change of volume and intensity of physical activity as predictors of hypertension. Scand J Publ Health 2004; 32: 303-309.

IV   Hernelahti M, Levälahti E, Simonen RL, Kaprio J, Kujala UM, Uusitalo-Koskinen ALT, Battié MC, Videman T. Relative roles of heredity and physical activity in adolescence and adulthood on blood pressure. J Appl Physiol 2004; 97: 1046-1052.

V   Hernelahti M, Tikkanen HO, Karjalainen J, Kujala UM. Muscle fiber-type distribution as a predictor of blood pressure: a 19-year follow-up study. Submitted.

The original publications are reproduced with the permission of the copyright holders.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
AIC	Akaike's information criterion
ATPase	adenosine triphosphatase
BMI	body mass index
BP	blood pressure
CI	confidence interval
DBP	diastolic blood pressure
DZ	dizygotic
FT	fast-twitch
ICC	intraclass correlation
LTPA	leisure-time physical activity
MET	metabolic equivalent
MZ	monozygotic
OR	odds ratio
PA	physical activity
RCT	randomized controlled trial
r_e	correlation of non-shared environmental factors
r_g	correlation of genetic factors
RR	risk ratio
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of mean
ST	slow-twitch
Type I%	proportion of type I muscle fibres

1. INTRODUCTION

Physical activity leads to numerous significant health benefits. Evidence exists for positive effects on all-cause mortality, on coronary heart disease, on blood pressure and hypertension, on blood lipids and lipoproteins, on type 2 diabetes, on obesity, and also on depression and anxiety. The occurrences of osteoporosis and colon cancer are reduced as well. Physical inactivity has been estimated to account for 35% of cardiovascular disease mortality in populations worldwide (Kesäniemi et al. 2001).

In Finland, nearly half of all deaths result from cardiovascular diseases (Statistics Finland 2003), for which one of the most important risk factors is hypertension (Kannel 1996, Kiiskinen et al. 1998, Domanski et al. 2001). In 2003, of 5.2 million Finns, about 491 000 had been granted the right to reimbursable medication for hypertension, this number increasing by 10 000 per year (according to the Prescription Register at the National Social Insurance Institution in Finland, http://www.kela.fi). Furthermore, hypertension is a serious risk factor for other cardiovascular diseases such as coronary heart disease, cardiac failure, stroke, and peripheral artery disease, and it shortens life-expectancy (Kannel 1996, Kiiskinen et al. 1998).

Thus, hypertension leads to considerable financial cost, and importantly, leads to a reduced quality of life. Thorough knowledge of the aetiology of hypertension may make it possible to prevent and treat the disease more efficiently. Hence, untangling of the association between physical activity and hypertension, made complex by genetic factors entwined with these factors, merits considerable scientific effort.

2. REVIEW OF THE LITERATURE

2.1. Physical activity

2.1.1. Definition of physical activity

Physical activity has been defined as 'any bodily movement produced by the skeletal muscles that results in a substantial increase over the resting energy expenditure' (Bouchard and Shephard 1994). Physical activity can be divided into occupational and leisure-time physical activity, whereas exercise signifies leisure-time physical activity that one is engaged in repeatedly in order to improve one's fitness or health, or to reach physical or mental well being (Bouchard and Shephard 1994).

2.1.2. Measurement of physical activity

Because physical activity is a complex and multidimensional exposure variable, population-based measurement of it is difficult. No gold standard field measure of physical activity exists (Kriska and Caspersen 1997, Lamonte and Ainsworth 2001). Doubly labelled water, consisting of stable water isotopes whose urinary excretion in the form of water and carbon dioxide is tracked, appears to be the most accurate field measure of energy expenditure, but is expensive and difficult (Lamonte and Ainsworth 2001). Moreover, physical activity accounts for only a portion of total energy expenditure, basal metabolic rate typically accounting for 50 to 70% of total energy expenditure, and can consist of totally different types of activities such as aerobic activities and weight training, which may have differing effects on health (Kriska and Caspersen 1997).

Assessment of physical activity also utilizes other objective measures such as motion detectors and heart rate monitors. These are much less costly and less difficult to use than doubly labelled water. They are, however, also rather expensive and not very practical in large epidemiological studies (Kriska and Caspersen 1997, Lamonte and Ainsworth 2001) but serve to validate physical activity questionnaires (Kriska and Kaspersen 1997).

Questionnaires are a relatively easy, inexpensive, and non-invasive method of assessing physical activity, but have limitations such as uncertainties in human recall and report bias (Lamonte and Ainsworth 2001). The validity of physical activity questionnaires is also often assessed by a comparison with maximal oxygen uptake. Considerable heterogeneity and familial aggregation in the responsiveness of fitness to regular physical activity, however, exist (Bouchard and Rankinen 2001), and fitness is at least in part determined by heredity (Paffenbarger et al. 1993, Blair and Brodney 1999, Rankinen et al. 2004). Difficulties in measuring health-related dimensions of physical activity limit the ability to detect significant associations between physical activity and disease outcomes (LaPorte et al. 1985, Powell et al. 1987, Kriska and Caspersen 1997).

2.1.3. Heritability of physical activity

The classical way to calculate heritability, i.e., the fraction of population variance due to genetic variance, is to compare the similarity of monozygotic (MZ) and dizygotic (DZ) co-twins according to the formula (Jensen 1967, Christian and Williams 2000):

$$\text{heritability}=2(r_{MZ}-r_{DZ})$$

The intra-class correlation coefficient (r) expresses the similarity of co-twins with respect to a specific variable (Christian and Williams 2000).

Participation in physical activity has a genetic component, the strongest evidence for which comes from twin studies (Kaprio et al. 1981, Slattery et al. 1988, Boomsma et al. 1989, Koopmans et al. 1994, Lauderdale et al. 1997, Beunen and Thomis 1999, Kujala et al. 2002, Maia et al. 2002). This hypothesis is also supported by family studies (Willerman and Plomin 1973, Pérusse et al. 1989, Sallis et al. 1988, Simonen et al. 2002). The magnitude of the estimation of the component varies greatly depending on the study; reports of the heritability of sports participation range from 0.35 to 0.83, and those of daily physical activity from 0.16 to 0.63 (Table 1). When available separately for males and females, the heritability estimates are approximately double for males (Table 1). The genetic component for high intensity exercise is higher than for moderate activity (Lauderdale 1997, Beunen and Thomis 1999, Maia et al. 2002, Kujala et al. 2002). These large variations in estimates may be explained by differences in assessment of physical activity and by analyses that are adjusted for body mass and other characteristics and thus lead to lower estimates of heritability (Beunen and Thomis 1999).

Table 1 Studies on heritability of physical activity

First author	Year	Subjects	Heritability estimate of PA or moderate-intensity activity	Heritability estimate of sports participation or vigorous-intensity activity
Kaprio	1981	1 537 MZ pairs and 3 507 DZ pairs	62%	
Slattery	1988	77 MZ pairs and 88 DZ pairs	27%	
Pérusse	1989	1610 subjects from 375 families	29%	
Boomsma	1989	44 MZ pairs, 46 DZ pairs, and their parents		35% (women) 77% (men)
Koopmans	1994	578 MZ pairs, 1 000 DZ pairs, and their parents		45%
Lauderdale	1997	1 006 MZ pairs and 530 DZ pairs	27%[a]	53%[b]
Beunen	1999	43 MZ pairs and 61 DZ pairs		44% (women) 83% (men)
Simonen	2002	312 parents and 384 offspring	16%	
Maia	2002	203 MZ pairs and 208 DZ pairs	32% (women) 63% (men)	40% (women) 68% (men)
Kujala	2002	1 772 MZ and 3 551 DZ pairs	45%[c]	55%[b]

PA, physical activity; MZ, monozygotic; DZ, dizygotic. Outcome variables: [a]moderate activities such as walking and stair climbing; [b]jogging or running; [c]total volume of physical activity.

2.1.3.1. Genetics of physical activity

Little data exist on specific genetic factors of physical activity levels in humans (Simonen et al. 2003a). In women but not in men, evidence is that physical activity levels are associated with polymorphisms in the dopamine D2 receptor gene, which is proposed to play a role in rewarding mechanisms (Simonen et al. 2003b), and with polymorphisms in the calcium-sensing receptor gene in part responsible for keeping serum calcium levels optimal (Lorentzon et al. 2001). To date, to the best of my knowledge, only one linkage study exists. It has found some promising loci that may be associated with participation in physical activity (Simonen et al. 2003a).

2.1.3.2. Muscle fibre-type distribution

Skeletal muscle consists of slow-twitch (ST, type I) and fast-twitch (FT, types IIa and IIb) muscle fibres. Fibre types can be determined on the basis of their myosin ATPase staining patterns (Brooke and Kaiser 1970) or on the basis of myosin heavy-chain isoform expression via electrophoresis (Reiser et al. 1985, Staron and Pette 1986). Type I fibres have slow and type II fibres have fast contraction velocities (Barnard et al. 1971, Burke et al. 1971). Type II fibres can be further classified into IIa and IIb fibres by ATPase staining. Type IIa are intermediate between type I and type IIb (Brooke and Kaiser 1970). Type I fibres have a higher oxidative capacity than type II (Essen et al. 1975). By myosin heavy-chain isoform expression, fast (type II) fibres are categorized into types IIa, IIb, and IIx in rodents, while only IIa and IIx are expressed in humans (Smerdu et al. 1994). Recently, however, findings show that myosin heavy chains can be expressed heterogeneously within a single muscle fibre (Talmadge et al. 1996, Pette and Staron 2000), but fewer than 5% of the fibres contain both the slow myosin I and fast myosin IIa isoform (Andersen et al. 2000).

In the vastus lateralis muscle, the percentage of type I fibres ranges from 13 to 96%, with a population mean of approximately 50% (Saltin and Gollnick 1983). High endurance performance is associated with a high proportion of type I fibres, and high speed and power capacities with a preponderance of type II fibres (Costill et al. 1976a, Costill et al. 1976b, Bergh et al. 1978). A high proportion of type I fibres is also associated with high physical activity levels (Tikkanen et al. 1998, 1999).

Muscle fibre type proportion is mostly determined by genetic factors. One twin study (Komi et al. 1977) (n=31 MZ and DZ pairs) reports as high heritabilities as 99.5% and 92.8% for males and females. Another (Bouchard et al. 1986) (n=61 MZ and DZ pairs) states that there are no genetic effects, but the authors later conclude, based on that study and animal studies, that the genetic variation component is 40 to 50% (Simoneau and Bouchard 1995). Furthermore, although some findings indicate that minor changes in fibre composition may occur with training, the current conclusion is that the composition is highly resistant to change along with alterations in aerobic activity (Bassett 1994, Simoneau and Bouchard 1995, Spangenburg and Booth 2003). Nor does muscle fibre-type distribution change with increasing age (Rogers and Evans 1993). Endurance training can, however, cause a shift within type II fibres from IIb to IIa (Bassett 1994).

2.2. Hypertension

2.2.1. Definitions of blood pressure and hypertension

Blood pressure signifies the intra-arterial pressure in the systemic circulation. With every heart-beat cycle, blood pressure varies between systolic and diastolic pressure. Systolic pressure is the maximum pressure produced by contraction of the heart, the systole, while diastolic pressure is the minimum pressure following the rest period of the heart, the diastole. Mean arterial pressure, calculated as (systolic pressure + 2 × diastolic pressure)/3, is the product of cardiac output and total peripheral resistance (Kaplan 1988).

Hypertension signifies elevated blood pressure, and its most recent WHO definition defines its lower limits as 140 mmHg systolic blood pressure and 90 mmHg diastolic blood pressure (Guidelines Subcommittee of WHO 1999). This definition is based on the relationship between blood pressure level and risk for cardiovascular events.

2.2.2. Physical activity and hypertension or blood pressure

2.2.2.1. Observational studies

A large number of observational studies addressing physical activity and hypertension or blood pressure have been conducted starting from the middle of the 20th century. In women, the first reports appeared as late as in the beginning of the 1980s. Most have revealed an inverse relationship between leisure-time physical activity and blood pressure levels or risk for hypertension both in men and in women. About half the studies controlled at least for age and body mass index. While the association was sometimes lost when adjusting for confounding factors, still more than half the studies reported a significant association between physical activity and blood pressure or risk for hypertension. Reduction in hypertension risk among the physically active has been on the order of 30%. The methods by which physical activity has been assessed vary, however, very much between studies (Tables 2-4), and most studies have not assessed aerobic, and anaerobic activity such as power and speed types, separately. Powell et al. (1987) found that the proportion of studies finding a significant association between physical activity and coronary heart disease depended on the quality of the tools for physical activity measurements. As this quality increased from unsatisfactory (40% of all studies) to satisfactory (40%) and good (20%), the proportion revealing an association increased from 50% to 78% and 88%.

To the best of my knowledge, no epidemiologic studies have compared low-intensity exercise with high-intensity exercise, but some studies have assessed risk for hypertension in those engaged in vigorous physical activity compared with those not engaged. In men, engagement in vigorous activity has been associated with low risk for hypertension (Paffenbarger et al. 1983, 1991, MacAuley et al. 1996, Haapanen et al. 1997b, Mensink et al. 1997, Pereira et al. 1999), while no association has been reported in women (Haapanen et al. 1997b, Mensink et al. 1997). Additionally, in regards to men, in those studies adjusting engagement in vigorous activity for total activity volume, vigorous activity lost its importance, while total volume was still associated with low risk for hypertension (Haapanen et al. 1997b, Mensink et al.

1997). As for volume of activity, very little data exist on any possible dose-response relationship.

In adolescents, little evidence exists for an association between physical activity early in life and a beneficial cardiovascular risk factor profile then or in adulthood (Aaron and LaPorte 1997, Twisk 2001, Twisk et al. 2002a). In four European cohort studies (Twisk et al. 2002b, Boreham et al. 2002, Hasselstrøm et al. 2002, Lefevre et al. 2002), physical activity was assessed at 12 to 19 years of age, and then, in each study, blood pressure was measured at ages 20 to 40 in the same subjects. Those studies found no association between physical activity in youth and low blood pressure in adulthood. One study (Barnekow-Bergkvist et al. 2001) did find a relationship between a positive attitude to aerobic exercise in adolescence and decreased risk for high systolic blood pressure in adulthood, 18 years later, but no diastolic pressure was reported. Leisure-time sports activity in adolescence was, however, not associated with low risk. One reason for discovering no association between physical activity in youth and a beneficial cardiovascular risk profile in adulthood may be difficulties in measuring physical activity (Twisk et al. 2002c).

Table 2 Observational studies on association between leisure-time physical activity and blood pressure or hypertension in men. All associations significant, p<0.05, unless otherwise stated.

First author	Year	Subjects	Age at baseline (years)	Design	Result	Adjusted for
Lange Andersen	1956	377 athletes and 652 controls; Norwegians	20 to >40	Cross-sectional	SBP and DBP lower in athletes than controls: in normal-weight men aged 20-29 133/83 vs. 136/89 mmHg	-
Raab	1965	200 American men	Mean 42.7	Cross-sectional	No significant differences in SBP or DBP in physically active and inactive	-
Doan	1966	225 American men	>35	Cross-sectional	No differences in SBP or DBP between most and least active members of YMCA with 'physical membership', allowing use of exercise facilities	-
Pyörälä	1967	61 former endurance athletes and 54 controls; Finns	41-78	Cross-sectional	SBP and DBP lower in former athletes than in controls: 137/87 vs. 147/92 mmHg	-
Saltin	1968	29 former and 33 still active endurance athletes	44-67	Cross-sectional	SBP non-significantly higher in still active than in former athletes; no difference in DBP	Age
Montoye	1972	1 361 Caucasian men	16 to >65	Cross-sectional	No association between LTPA and SBP or DBP	-
Berglund	1974	493 Swedish men with SBP 160-175, DBP 95-115 mmHg	47-55	Follow-up, 2 years	Non-significant trend for low LTPA as being associated with increased blood pressure or medication for hypertension at follow-up	-
Berglund	1975	7 263 Swedish men	47-54	Cross-sectional	No association between LTPA and SBP or DBP; more antihypertensive medication in those with low PA at work or during leisure time	-
Hickey	1975	15 171 Irish men	25-74	Cross-sectional	SBP and DBP lower in subjects with heavy LTPA than in those with minimal LTPA: 125/80 vs. 138/85 mmHg	-
Fardy	1976	350 former competitive athletes and 156 controls; Americans	27-74	Cross-sectional	No difference in SBP or DBP between former athletes and controls	-
Aromaa	1981	14 326 Finnish men	30-59	Cross-sectional	No association between LTPA and SBP or DBP	-
Arkwright	1982	499 Caucasian men	20-45	Cross-sectional	No association between LTPA and SBP or DBP	Several variables

Paffenbarger	1983	14 998 American men	35-74	Follow-up, 6-10 years	No vigorous sports play associated with high risk for hypertension (RR 1.35); in analyses stratified for BMI, this increase in risk is evident only in overweight subjects (BMI >25.3); low energy expenditure (<2000 kcal/week) associated with high risk (RR 1.30)	Age
Lehmann	1984	810 German sportsmen	14-69	Cross-sectional	Higher incidence of hypertension (measured BP) in weight lifters and swimmers than in endurance athletes and ball-game players	Age
Folsom	1985	738 Caucasian men	25-74	Cross-sectional	No association between LTPA and SBP or DBP	Age
Svedenhag	1986	10 long-distance runners and 10 untrained men; Swedes	Mean 35.2	Cross-sectional	DBP lower in runners than in untrained: 76 vs. 84 mmHg; no difference in SBP	-
Cederholm	1986	371 Swedish men	47-54	Cross-sectional	Lower SBP and DBP in men with high LTPA than in those with low LTPA: 134/84 vs. 131/82 mmHg; trend for association between LTPA and prevalence of hypertension (significant with sexes combined)	-
Jenner	1988	340 Australian men	20-45	Follow-up, 6 years	Increased or sustained involvement in sport during follow-up associated with low increases in SBP and DBP during follow-up; for SBP, association persisted after adjustments	Several variables
Slattery	1988	330 men; Americans	22-66	Cross-sectional	No association between LTPA and SBP or DBP	Age
Paffenbarger	1991	5 463 men; Americans	40-54	Follow-up, 14 years	Men engaged habitually in vigorous sports play at 19-29% less risk for hypertension than men with no sports play; student sports play not associated with risk in middle age	Age
Klesges	1991	221 Caucasian men	23-52	Cross-sectional	No association between LTPA and SBP or DBP	-
Ainsworth	1991	655 black men; Americans	25-50	Cross-sectional	Sedentary behaviour not associated with prevalence of hypertension	Several variables
Joffres	1992	10 104 Canadian men	18-74	Cross-sectional	Sedentary lifestyle more prevalent in hypertensives than normotensives: 42 vs. 37%	Age
Burke	1992	505 Australian men	60-87	Cross-sectional	High LTPA associated with low SBP and DBP	Several variables
Young	1993	380 American men	18-74	Follow-up, 5 years	No association between change in LTPA and change in SBP	-
Staessen	1994	405 Belgian men	20-84	Cross-sectional	High energy expenditure in sports associated with low DBP but not SBP: 1.5 mmHg lower DBP in most active tenth than in least active tenth	Several variables

Kujala	1994	1 282 former elite athletes (175 endurance, 664 mixed sports, 443 power sports athletes) and 777 controls; Finns	36-94	Cross-sectional	Age-adjusted risk for hypertension lower in former endurance (OR 0.53) and mixed sports athletes (OR 0.72) than in controls; when adjusted also for BMI, non-significant trend for low risk in endurance and mixed sports, and low risk in power sports (OR 0.70)	Several variables
MacAuley	1996	305 men from Northern Ireland	16-74	Cross-sectional	High LTPA associated with low SBP and DBP unadjusted; adjusted, only past participation in sports associated with low DBP	Several variables
Haapanen	1997	731 Finnish men	19-63	Follow-up, 10 years	High risk for hypertension in subjects not engaged in vigorous activity (RR 1.56), or with low total energy expenditure (RR 1.73), age-adjusted; when further adjusted for BMI and diabetes, marginally non-significant	Several variables
Mensink	1997	5 943 German men	25-69	Cross-sectional	High volume of high intensity activities associated with low DBP but not SBP	Several variables
Masaki	1997	1 378 Japanese-American men	60-82	Cross-sectional	No association between LTPA and SBP or DBP	Several variables
Pihl	1998	84 former endurance athletes (44 presently active, 40 inactive) and 84 controls (41 active, 43 inactive); Estonians	40-50	Cross-sectional	Lower SBP in active former athletes than in inactive athletes or inactive controls; lower DBP in active former athletes than in inactive athletes; higher DBP in inactive athletes than active controls	-
Williams	1998	5 915 endurance runners; Americans	Mean 45.7	Cross-sectional	High number of km run per week associated with low risk for hypertension; no association when adjusted for times in 10 km running race	Several variables
Pereira	1999	2 912 white and 475 black Americans	45-64	Follow-up, 6 years	High LTPA at baseline associated with low risk for hypertension during follow-up in white but not in black men	Several variables
Hayashi	1999	6 017 Japanese men	35-60	Follow-up, 4 years	Low risk for hypertension during follow-up with LTPA at least once a week compared with less (RR 0.70)	Several variables
Wareham	2000	334 British men	45-70	Cross-sectional	Association between high energy expenditure and low SBP and DBP: 132/80 vs. 138/85 mmHg in highest vs. lowest energy expenditure group (adjusted for age and treatment); the association significant also after adjusting for BMI	Several variables
Carroll	2000	697 Caucasian men	Mean 46.9	Cross-sectional	High LTPA associated with low SBP and DBP: 125/81 vs. 131/86 mmHg in highest vs. lowest LTPA group	Age
Katzmarzyk	2000	781 Canadian men	7-69	Follow-up, 7 years	No association between baseline LTPA and SBP or DBP at follow-up	Several variables

Byberg	2001	898 Swedish men	46-50 and 67-71	Cross-sectional	No association between LTPA at 50 or at 70 years of age	Age and BMI
Levenstein	2001	1 031 American men	Adults	Follow-up, 20 years	No association between LTPA at baseline and risk for hypertension during follow-up	Several variables
Tsutsumi	2001	3 187 Japanese men	18-65	Cross-sectional	High LTPA associated with low prevalence of hypertension: LTPA coded 1-3, adjusted OR for hypertension per increasing class 0.87	Several variables
Sobngwi	2002	1 048 men from Cameroon	20-60	Cross-sectional	In urban men, high LTPA associated with low SBP and DBP; in rural men, high LTPA associated with low SBP but not DBP	-
Hu	2004	8 302 Finnish men	25-64	Follow-up, 11 years	High physical activity (LTPA not separated) associated with low risk for hypertension (hazard ratio 0.59 for high level vs. low level of physical activity)	Several variables

SBP, systolic blood pressure; DBP, diastolic blood pressure; LTPA, leisure-time physical activity; PA, physical activity; BMI, body mass index; RR, risk ratio; BP, blood pressure; OR, odds ratio

Table 3 Observational studies on association between leisure-time physical activity (LTPA) and blood pressure or hypertension in women. All associations significant, p<0.05, unless otherwise stated.

First author	Year	Subjects	Age at baseline (years)	Design	Result	Adjusted for
Aromaa	1981	11 758 Finnish women	30-59	Cross-sectional	No association between LTPA and SBP or DBP	-
Folsom	1985	878 Caucasian women	25-74	Cross-sectional	High energy expenditure in heavy exercise associated with low SBP	Age
Cederholm	1986	436 Swedish women	47-54	Cross-sectional	No association between LTPA and SBP or DBP; trend for association between LTPA and prevalence of hypertension (significant with men and women combined)	-
Folsom	1990	2 126 Caucasian women	55-69	Follow-up, 2 years	High level of LTPA associated with 30% reduction in risk for hypertension	Age
Reaven	1991	641 Caucasian women	50-89	Cross-sectional	Intensity of LTPA associated with SBP and DBP: 128/72 vs. 137/75 mmHg for high intensity LTPA vs. no LTPA groups	Several variables
Klesges	1991	221 Caucasian women	23-52	Cross-sectional	High LTPA associated with low SBP and DBP	-
Ainsworth	1991	1 096 black women	25-50	Cross-sectional	Sedentary behaviour associated with high prevalence of hypertension (OR 1.59)	Several variables
Joffres	1992	10 463 Canadian women	18-74	Cross-sectional	Sedentary lifestyle more prevalent in hypertensives than in normotensives: 39 vs. 34%	Age
Burke	1992	338 Australian women	60-87	Cross-sectional	High LTPA associated with low SBP and DBP in women treated for hypertension but not in those untreated (including both normotensives and hypertensives)	Several variables
Young	1993	427 women	18-74	Follow-up, 5 years	Change in LTPA inversely correlated with change in SBP in pre- but not in postmenopausal women	-
Staessen	1994	379 Belgian women	20-84	Cross-sectional	High energy expenditure in sports associated with low SBP and DBP: 2.4 and 1.8 mmHg lower in most active tenth than in least active tenth	Several variables
Rauramaa	1995	127 Finnish women	60-69	Cross-sectional	Lower DBP in most active women than in least active women: 86 vs. 94 mmHg; non-significant trend for SBP	BMI
MacAuley	1996	299 women from Northern Ireland	16-74	Cross-sectional	High LTPA associated with low SBP and DBP unadjusted; no association when adjusted	Several variables
Bijnen	1996	934 Finnish, Italian and Dutch men	69-90	Cross-sectional	No association between LTPA and SBP or DBP, nor between LTPA and prevalence of hypertension	Several variables
Haapanen	1997	796 Finnish women	19-63	Follow-up, 10 years	No association between LTPA and risk for hypertension	Several variables

Mensink	1997	6 039 German women	25-69	Cross-sectional	High volume of high-intensity activities associated with low SBP but not DBP	Several variables
Stevenson	1997	18 active distance runners and 34 sedentary controls; Caucasians	49-70	Cross-sectional	Trend for lower DBP values in runners than in controls; no difference in SBP	-
Pihl	1998	63 former endurance athletes (34 presently active, 29 inactive) and 84 controls (39 active, 45 inactive); Estonians	40-50	Cross-sectional	Lower SBP in active former athletes and active controls than in inactive controls; lower SBP in inactive former athletes than in inactive controls; no differences in DBP	-
Williams	1998	1 449 endurance runners; Americans	Mean 40.6	Cross-sectional	No association between number of km run per week and SBP or DBP	Several variables
Pereira	1999	3 339 white and 713 black Americans	45-64	Follow-up, 6 years	No association between LTPA and risk for hypertension	Several variables
Wareham	2000	441 British women	45-70	Cross-sectional	Association between high energy expenditure and low SBP and DBP: 121/72 vs. 132/78 mmHg in highest vs. lowest energy-expenditure group (adjusted for age and treatment; the association significant also after adjusting for BMI	Several variables
Amigoni	2000	22 919 Italian women	44-66	Cross-sectional	Low risk for hypertension in women with high LTPA compared with low LTPA (OR 0.7)	Several variables
Katzmarzyk	2000	722 Canadian women	7-69	Follow-up, 7 years	High LTPA at baseline associated with low SBP and DBP at follow-up	Several variables
Levenstein	2001	1 326 American women	Adults	Follow-up, 20 years	High LTPA at baseline associated with low risk for hypertension during follow-up	Several variables
Räikkönen	2001	490 white and 48 black Americans	42-50	Follow-up, 1-14 years	High LTPA at baseline associated with low risk for hypertension during follow-up; significance lost when adjusted for multiple variables	Several variables
Tsutsumi	2001	3 400 Japanese women	18-65	Cross-sectional	High LTPA marginally non-significantly associated with low risk for hypertension	Age
Sobngwi	2002	1 417 women from Cameroon	20-58	Cross-sectional	No association between LTPA and SBP or DBP	-
Hu	2004	9 139 Finnish women	25-64	Follow-up, 11 years	High physical activity (LTPA not separated) associated with low risk for hypertension (hazard ratio 0.72 for high vs. low level of physical activity)	

LTPA, leisure-time physical activity; SBP, systolic blood pressure; DBP, diastolic blood pressure; OR, odds ratio

Table 4 Observational studies on association between leisure-time physical activity (LTPA) and blood pressure or hypertension. Analyses in men and women not separated. All associations significant, p<0.05, unless otherwise stated.

First author	Year	Subjects	Age at baseline (years)	Design	Result	Adjusted for
Moore	1990	3 019 men and 3 698 women; Americans	>18	Cross-sectional	High LTPA associated with low DBP but not SBP	-
Yang	1996	479 Taiwanese men and women	>20	Cross-sectional	High LTPA associated with low risk for hypertension	Several variables
Davidson	2000	870 white men, 936 white women, 633 black men and 904 black women; Americans	23-35	Follow-up, 5 years	High risk for hypertension during follow-up for physically inactive at baseline in black (OR 1.73) but not in white subjects	Several variables
Bassett	2002	6 436 white, 4 244 black and 4 219 Hispanic Americans	18 to >80	Cross-sectional	High LTPA associated with low risk for hypertension in whites and blacks, but not in Hispanics; OR for subjects exercising moderately or vigorously: 0.73 for whites and 0.73 (marginally non-significant) for blacks compared with subjects with no LTPA	Several variables
Jenei	2002	19 961 Hungarians	30-65	Cross-sectional	Low LTPA associated with high risk for hypertension: OR 1.26 for low LTPA compared with high LTPA	Several variables
Fuentes	2002	167 men and 288 women; Finns	35-55	Cross-sectional	High LTPA associated with low DBP, but not SBP; the association was lost when adjusted for multiple variables	Several variables
Fang	2003	9 790 white and black American men and women	25-55	Cross-sectional	Prevalence of self-reported hypertension or BP ≥160/95 mmHg 56%, 46%, and 45% in groups with much, moderate, and little or no recreational exercise by self-assessment	-
Felmeden	2003	198 men and 36 women with hypertension, and 46 men and 14 women who were healthy, mostly white; British	40-80	Cross-sectional	Low LTPA associated with low DBP but not SBP among hypertensives; no difference in LTPA between hypertensives and normotensives	-
Franks	2004	295 men and 392 women; British	Mean 57	Cross-sectional	Physical activity energy expenditure inversely related to SBP and DBP	Several variables

LTPA, leisure-time physical activity; DBP, diastolic blood pressure; SBP, systolic blood pressure; OR, odds ratio; BP, blood pressure

2.2.2.2. Intervention studies

Aerobic physical activity lowers blood pressure in both normotensives and hypertensives: The training-induced net changes were on average -3.8/-2.6 mmHg for systolic/diastolic blood pressure. In trials where subgroups regarding hypertensive status were defined, the net changes averaged -4.0/-2.3 mmHg in normotensives and -4.9/-3.7 mmHg in hypertensives, and these effects of aerobic exercise seem to be independent of change in body weight (Whelton et al. 2002). Exercise training-induced reductions in blood pressure seem to be larger and more consistent in women than in men (-14.7/-10.7 mmHg in women vs. -8.7/-7.8 mmHg in men in absolute reductions) (Hagberg et al. 2000).

A large variation appears between individuals in resting blood pressure response to exercise training. The response of systolic blood pressure is familially aggregated, the maximal heritability as being 18%, whereas the response of diastolic pressure is reported not to be heritable but environmentally determined (Rice et al. 2002). Nitric oxide synthase 3 (NOS3) (Kimura et al. 2003), angiotensin I-converting enzyme (ACE) (Hagberg et al. 1999, Zhang et al. 2002), and angiotensinogen M235T (Rauramaa et al. 2002) polymorphisms have been suggested to explain part of this variation and heritability.

Interestingly, weekly frequency (3-5 sessions per week), time per session (30-60 min per session), exercise intensity (40-70% of net maximal exercise performance) or total net energy expenditure per week do not seem to be related to the magnitude of the changes in blood pressure (Fagard 2001, Whelton et al. 2002), indicating that it is not important how one exercises as long as one does exercise. However, seven sessions per week may elicit a slightly larger decrease in blood pressure than three sessions per week (Jennings et al. 1986, Nelson et al. 1986, Fagard 2001). One problem in establishing the dose response between physical activity and reduction in blood pressure is the lack of knowledge of cellular and subcellular mechanisms of the effect (Haskell 2001).

Several short sessions of physical activity per day, that is, fractionization of exercise, seem to be as effective as one long session in improving cardiorespiratory fitness or postprandial plasma triglyceride concentrations (Hardman 2001). Although reports are lacking as to fractionization of exercise as a treatment for hypertension, cardiorespiratory fitness is assumed to be a health outcome because of lower cardiovascular and all-cause mortality in men and women with higher levels of fitness (Blair et al. 1996, Hardman 2001).

2.2.2.3. Mechanisms by which training reduces blood pressure

The mechanisms of the training-induced blood pressure changes are largely unknown (Fagard 1999). Blood pressure is the product of cardiac output and total peripheral resistance (Kaplan 1988), and both a reduction in systemic vascular resistance and a decrease in cardiac output have been suggested as being behind the reduction in blood pressure.

With training, a decrease in total peripheral resistance and an increase in cardiac output at rest, with the sum effect of decreased blood pressure, have been found in many studies. In these studies, the plasma noradrenaline concentration and noradrenaline spillover rate into plasma (an index of sympathetic activity) plus total peripheral resistance, and thus blood pressure, dropped with endurance training (Jennings et al. 1986, Nelson et al. 1986, Hagberg et al. 1989, Meredith et al. 1990, 1991). Peripheral resistance, and thus blood pressure, had, however, already decreased after 2 weeks of exercise, whereas plasma noradrenaline concentration decreased after 4 weeks of exercise, indicating that the initial fall in blood pressure may not be due to a reduction in sympathetic activity (Meredith et al. 1990). The reduction in noradrenaline spillover rate was predominantly renal; there occurred no reduction in cardiac spillover (Meredith et al. 1991). The increase in renal vascular conductance constituted, however, only a fraction of the increase in total peripheral resistance, indicating that other effects of inhibition of renal sympathetic activity such as decreased release of renin may be important (Meredith et al. 1991). Moreover, urinary noradrenaline output in one observational study was lower in exercisers than in nonexercisers (Palatini et al. 1994). Results on the effects of endurance training on plasma levels of renin and angiotensin II, and on plasma or urinary aldosterone are inconsistent (Fagard 1995).

There are, however, also several studies reporting a fall in cardiac output at rest (Kinoshita et al. 1988, Seals and Reiling 1991, Hagberg et al. 1989). In those studies where plasma noradrenaline was measured (Kinoshita et al. 1988, Hagberg et al. 1989), its concentration decreased. Haemodynamic data are conflicting, perhaps due to differing methods and problems with non-invasive measurement of cardiac output (Fagard and Tipton 1994).

Exercise training induces a systemic increase in peak limb vascular conductance, meaning that when one limb is trained and the other is untrained, conductance increases in both trained and untrained limbs (Martin et al. 1991, Kingwell et al. 1997, Tanaka et al. 1998). Peak limb vascular conductance correlates with the media : lumen ratio of arterial resistance vessels (Agabiti Rosei et al. 1995), a ratio known to be associated with hypertension (Folkow 1995), but is also strongly influenced by endothelial function (Tanaka et al. 1998, Higashi et al. 1999a). Training restores the endothelial function (Higashi et al. 1999a) which is impaired in hypertension (Linder et al. 1990, Panza et al. 1990). Endurance athletes also have better endothelial function than do their sedentary controls (Kingwell et al. 1996). Endothelial function is improved with training through an increased release of nitric oxide (Higashi et al. 1999b). In intervention studies, a reduction in resting blood pressure appeared together with improved endothelial function (Kingwell et al. 1997, Tanaka et al. 1998, Higashi et al. 1999a, Higashi et al. 1999b).

Training induces structural adaptations in the arterial vascular system. The diameter of the femoral artery has been found to be larger, with a higher distensibility, in well-trained cyclists than in sedentary controls, but no significant difference in blood pressure appeared between these two groups (Kool et al. 1992). Hammer throwers have larger radial arteries, with a higher compliance, in the more highly trained arm than in the contralateral arm, or in the arms of sedentary controls (Giannattasio et al 1992). Long-distance runners and professional cyclists have larger great and medium

caliber arterial and venous vessels than do controls (Zeppilli et al. 1995). Further, endurance-orientated unilateral training leads to a considerable increase in capillary density of the trained muscle groups over that of the corresponding contralateral muscle groups (Saltin 1985). Hypertensives have a lower capillary density than do normotensives (Henrich et al. 1988, Hedman et al. 2000) and the increase in blood pressure from 50 to 70 years of age has been strongly inversely associated with capillary density (Hedman et al. 2000).

Finally, blood volume expansion resulting from exercise training, found to be around 7% in training studies and from 20 to 25% in highly trained athletes (Convertino 1991), is sufficient to cause an elevated discharge from low-pressure baroreceptors in the right atrium (O'Sullivan 2000), which leads to withdrawal of sympathetic vasomotor tone (Tanaka et al. 1999) and thus a lowering of total peripheral resistance and decreased blood pressure at rest (Kaplan 1988, O'Sullivan 2000). There also exist findings that plasma volume is decreased in hypertensive patients along with a decrease in blood pressure, without any change in urinary sodium excretion (Urata et al. 1987, Kinoshita et al. 1988).

2.2.2.4. Postexercise hypotension

Blood pressure acutely decreases immediately after a single bout of aerobic exercise lasting 30 to 60 minutes at intensities greater than 40% of maximal aerobic capacity (Kenney and Seals 1993, Halliwill 2001). The pressure reductions have been on average 6 to 11 mmHg in systolic and 4 to 9 mmHg in diastolic pressure, being more marked in hypertensives than in normotensives (Kenney and Seals 1993), whereas the mean change in blood pressure after acute exercise was -2.1/-0.3 mmHg by ambulatory measurements (Thompson et al. 2001). Sedentary and endurance-trained subjects exhibit similar degrees of blood pressure reductions (Senitko et al. 2002). The effect persists from 2 to 4 hours up to 13 hours after exercise, and seems to be longer among hypertensives than among normotensives (Pescatello et al. 1991, Kenney and Seals 1993). The effect is due to a drop in systemic vascular resistance during exercise, which is not restored to normal level as rapidly as is the exercise-induced increase in cardiac output. This is achieved by reduced activity of the sympathetic nervous system and impaired vascular responsiveness to α-adrenergic receptor stimulation, possibly through increased production of nitric oxide (Halliwill 2001). In endurance-trained men, however, postexercise hypotension has been the result of reduced cardiac output with vasodilation absent (Senitko et al. 2002). The extent to which chronic pressure-lowering effects of aerobic exercise reflect a carryover of the acute effects of exercise is unknown (Halliwill 2001).

2.2.2.5. Occupational physical activity

The relation between physical activity and blood pressure was first usually studied with regard to occupational physical activity, and heavy physical activity at work was, in men, associated with low blood pressure (Humerfelt and Wedervang 1957, Miall and Oldham 1958) and with low prevalence of hypertension (Morris 1959). Later studies have generally found no association between occupational physical activity and blood pressure (Klesges et al. 1991, Stender et al. 1993, Staessen et al. 1994) or risk for hypertension (Cederholm and Wibell 1986, Pereira et al. 1999, Felmeden et

al. 2003) in men or in women. One study (Xu et al. 1997) reports an inverse association between work exertion and blood pressure in rural Chinese women but not in men, and one study (Sobngwi et al. 2002) reports occupational activity as being inversely associated with blood pressure in rural men in Cameroon, but not in the women or in urban men.

2.2.2.6. Fitness

Physical activity is difficult to quantify objectively. Maximal physical working capacity (aerobic or endurance fitness) can be assessed with a higher precision than can physical activity, and has been used as a marker for physical activity (Paffenbarger et al. 1993, Blair and Brodney 1999). There is, however, considerable heterogeneity and familial aggregation in the responsiveness of fitness to regular physical activity (Bouchard and Rankinen 2001). Fitness is in part determined by genetic factors, and furthermore, measurement of fitness is expensive and logistically complicated to perform in epidemiological studies (Paffenbarger et al. 1993, Blair and Brodney 1999).

High-level physical fitness is associated with low systolic and diastolic blood pressure in both men (Gyntelberg and Meyer 1974, Cooper et al. 1976, Hartung et al. 1990) and women (Gibbons et al. 1983, Hartung et al. 1990). High-level fitness has also been able to predict low risk for hypertension in men and women (Blair et al. 1984). In one questionnaire study, Williams (1998) found an association between high endurance performance, measured as a respondent's best time in a 10-km foot-race during the previous 5 years, and low blood pressure. Endurance performance was also more strongly associated with risk for hypertension than was volume of physical activity, measured as weekly running distance.

2.2.3. Other environmental risk factors for hypertension

Overweight and obesity
Overweight is strongly associated with hypertension (Stamler et al. 1978, Havlik et al. 1983), and is an important predictor of hypertension (Paffenbarger et al. 1983). Weight gain predicts, independently of baseline weight, risk for hypertension (Paffenbarger et al. 1983, Ashley et al. 1974). Weight loss is, in fact, an effective treatment for hypertension (Andrews et al. 1982).

It has been suggested that obesity leads to hypertension via an increase in activity of the sympathetic nervous system (Rumantir et al. 1999, Esler 2000), an increase known to be associated with hypertension (Mancia 1997, Esler 2000). There are, however, also indications for hypertension's inducing obesity through increased sympathetic activity and downregulation of β-adrenergic receptors, making it difficult for hypertensives to lose weight (Julius et al. 2000). Other mechanisms through which obesity may lead to hypertension include insulin resistance (Rocchini et al. 1989), increased activity of the renin-angiotensin system (Tuck et al. 1981), and a pathologically low variability in cortisol secretion, including high stress-related secretion (Rosmond et al. 1998, Rosmond et al. 2000). All of these mechanisms can lead to increased sodium and fluid retention and thus to increased blood pressure (Rocchini 2002).

Diet

High salt intake, assessed as 24-hour urinary sodium excretion, is associated with high blood pressure both in individuals (Frost et al. 1991, Elliot et al. 1996) and in populations (Law et al. 1991, Elliot et al. 1996). Moreover, in a Chinese population living relatively isolated, who consume a diet low in sodium content, hypertension is virtually absent. Migration to urban areas, and a change in diet to a higher content of sodium leads, however, to an increase in blood pressure with age, and an increase in prevalence of hypertension (He et al. 1991). Further, a reduced dietary sodium intake has been associated with reduction in blood pressure for both hypertensives and normotensives (Midgley et al. 1996, Cutler et al. 1997)

Blood pressure does not increase in all individuals with increased ingestion of sodium. A gaussian distribution is evident in the blood pressure responses to changes in sodium intake, with hypertensives being, on average, more salt sensitive, i.e., more sensitive to an increase in salt intake, than are normotensive individuals (Weinberger et al. 1996). In young persons with hypertension, salt sensitivity is less common than in those older (Weinberger et al. 1996, Midgley et al. 1996). Obese individuals are more salt sensitive than nonobese ones, and loss of weight reduced their salt sensitivity (Rocchini et al. 1989).

Salt-sensitive hypertension has been proposed to develop via microvascular and tubulointerstitial injury in the kidneys, causing a rightward shift in the pressure-natriuresis curve (Guyton et al. 1972, Cowley et al. 1996), leading to the higher blood pressure needed to excrete a given amount of sodium, and this leads to hypertension in the presence of a high intake of salt (Johnson et al. 2002a). Other hypotheses include: an abnormal renin-angiotensin-aldosterone system in which abnormally low levels of renin and aldosterone accompany low sodium intake, low levels of atrial natriuretic factor after a high salt intake, abnormalities in ion transport, and hyperinsulinemia; all these four cause retention of sodium and water on a high sodium diet (Haddy et al. 1995, Weinberger et al. 1996). Sodium retention in turn leads to production of Na^+-K^+-ATPase inhibitors, ouabain-like substances that elevate intracellular calcium, stimulating heart contractility and arteriolar vasoconstriction, and thus increasing peripheral vascular resistance (Blaustein et al. 1991, Haddy et al. 1995, Johnson et al 2002b).

Potassium intake is negatively correlated with blood pressure, and potassium supplementation is associated with a decrease in blood pressure (Intersalt Co-operative Research Group 1988). Its effects are enhanced when a simultaneous high intake of sodium occurs (Whelton et al. 1997). The effect of potassium is suggested to be due to natriuresis, to increased urinary kallikrein, and to vasodilation via stimulation of Na^+-K^+-ATPase in vascular smooth muscle cells and adrenergic nerve terminals (Haddy et al. 1995). Calcium supplementation lowers systolic, but not diastolic, blood pressure, but the effect is too small to support a recommendation for calcium supplementation (Allender et al. 1996). Magnesium supplementation does not result in significant blood pressure reductions (Trials of Hypertension Prevention Collaborative Research Group 1992, He et al. 1997).

There are some indications of a beneficial effect of omega-3-polyunsaturated fatty acids, dietary fibres, and protein on blood pressure, but more and better studies are needed (He et al. 1997).

Alcohol
A positive relation between alcohol consumption and blood pressure has been apparent both cross-sectionally (MacMahon 1987, Intersalt Co-operative Research Group 1988, Marmot et al. 1994, Stamler et al 1997) and prospectively (Stamler et al. 2002, Thadhani et al. 2002). There exists some evidence of a threshold in the relationship between alcohol intake and blood pressure. The large Intersalt study (Marmot et al. 1994) found a weak relation at levels below 300 ml/week, corresponding to about 34 g alcohol per day, the equivalent of three or four drinks, and a strong relation at a higher intake. Other studies have found conflicting results regarding this threshold (Klatsky et al. 1977, Dyer et al. 1977). For women, more evidence suggests a threshold at about 1.5 drinks per day (Thadhani et al. 2002). Reduction in alcohol consumption is associated with reduction in blood pressure, a relationship found to be dose-dependent (Xin et al. 2001).

Both direct alcohol-mediated and withdrawal effects have been considered responsible for elevated blood pressure (Saunders et al 1981, Potter et al 1984, Abe et al. 1994, Rosito et al. 1999). A single drink has a blood pressure-lowering effect, while repeated intake results in increased blood pressure (Abe et al. 1994). Alcohol enhances sympathetic nervous activity and thus raises blood pressure, but dexamethasone suppresses this effect (Randin et al. 1995). High plasma renin and plasma cortisol levels, as well as increased vasoconstrictor sensitivity of the blood vessels have been suggested to be elevated with alcohol intake (MacMahon 1987).

Insulin resistance
Hypertension is associated with insulin resistance independently of obesity (Ferrannini et al. 1987, Pollare et al. 1990, Ferrannini et al 1997), with hypertension approximately twice as frequent in patients with type II diabetes as in persons without it (Sowers et al. 2001). A causal relationship between insulin resistance and hypertension is likely. This hypothesis is supported by several types of studies. The prevalence of insulin resistance is not higher in patients with secondary forms of hypertension (Marigliano et al. 1990, Shamiss et al. 1992). Moreover, plasma insulin concentrations, fasting and after intravenous glucose, are independent predictors of the development of hypertension (Skarfors et al. 1991, Lissner et al. 1992). Only about half the hypertensives are, however, insulin resistant (Ferrannini et al. 1987, Zavaroni et al. 1992), which may in part explain why several population studies have found no association between insulin resistance and hypertension (Reaven 2003).

In insulin-resistant subjects, the endothelium-dependent vasodilation mediated by nitric oxide and normally induced by insulin is lost (Steinberg et al. 1996). Insulin can also enhance renal sodium retention by its direct effects on renal tubules and by its stimulation of the sympathetic nervous system (Rocchini et al. 2002, Imazu 2002). Moreover, angiotensin II seems to play a key role in the association between hypertension and insulin resistance: It inhibits insulin signalling, resulting in inhibition of the vasodilation and glucose-transport properties of insulin and may also increase myosin light-chain activation, leading to vasoconstriction (Sowers 2004).

Socioeconomic factors

Working-class populations have shown a high prevalence of hypertension (Lang et al. 1997, de Gaudemaris et al. 2002). A low educational level is also associated with increased prevalence of hypertension (The HDFP Cooperative Group 1977, Dyer et al. 1976, Hoeymans et al. 1996), this relationship possibly as being more pronounced in women than in men (Haglund 1985, van Rossum et al. 2000). A low education and socioeconomic status are also prospectively associated with increased incidence of hypertension (Keil et al. 1981). Use of alcohol and obesity are related to socioeconomic factors (Niedhammer et al. 1998, Wamala et al. 1997, de Gaudemaris et al. 2002), and may be considered as being mediating factors between social inequalities and hypertension (Hoeymans et al. 1996, de Gaudemaris et al. 2002).

2.2.4. Inherited factors and hypertension

Heritability of blood pressure and hypertension

A large number of studies concerning genetic effects behind systolic and diastolic blood pressure demonstrate that blood pressure is in part determined genetically (Fagard et al. 1995, Luft 2001). The strongest evidence for this hypothesis comes from twin studies (Slattery et al. 1988, Hunt et al. 1989, Hong et al. 1994, Fagard et al. 1995, Snieder et al. 2000, Vinck et al. 2001, Iliadou et al. 2002, Evans et al. 2003). The hypothesis is also supported by studies on adopted children (Biron et al. 1976, Mongeau et al. 1986, Rice et al. 1989, Iliadou et al. 2002) and by family studies (Hunt et al. 1989, Schork et al. 1994, An et al. 1999, Livshits et al. 2001). Estimates of the proportion of variation in blood pressure explained by genes show wide variation, ranging from 15 to 66% (Table 5). One large (4 307 MZ pairs and 9 581 DZ pairs) twin study (Koskenvuo et al. 1992) investigated heritability of incident hypertension during 10 to 12 years of follow-up; heritability of hypertension was 50% for those under 60, and 33% for those over 60.

Table 5 Studies on heritability of blood pressure

First author	Year	Subjects	Heritability estimate of blood pressure	
			Systolic	Diastolic
Mongeau	1986	756 adopted and 445 natural children, 1176 parents	61%	58%
Slattery	1988	77 MZ pairs and 88 DZ pairs	60%	66%
Rice	1989	1 560 individuals from 374 families; parents, twins, singletons, and adoptees	16%	34%
Hunt	1992	146 MZ and 162 DZ twins, 1 102 adults in 67 pedigrees	62% (twins) 15% (pedigrees)	65% (twins) 25% (pedigrees)
Hong	1994	289 twin pairs reared apart or together	44%	34%
Schork	1994	5 376 subjects in 2 184 households	17%	13%
Fagard	1995	26 MZ pairs and 27 DZ pairs	63%	55%
An	1999	528 subjects in 98 families	54%	41%
Snieder	2000	225 MZ and 594 DZ pairs	17%	22%
Vinck	2001	150 MZ and 122 DZ pairs	49%	49%
Livshits	2001	514 subjects in 135 families	51%	20%
Iliadou	2002	106 MZ and 192 DZ pairs reared apart or together	39-46%	38-63%
Evans	2003	1 884 MZ pairs and 2 490 DZ pairs	44-66%	52-66%

MZ, monozygotic; DZ, dizygotic

The large variation in these estimates may be due to random errors in single measurements or the white-coat effect on blood pressure measurement under clinical conditions (Fagard et al. 1995, Whitlock et al. 2001). Such effects on variation can be reduced by use of ambulatory blood pressure measurements, by which heritability estimates have been 49 to 63% for systolic and 49 to 55% for diastolic blood pressure during the awake daytime period (Fagard et al. 1995, Vinck et al. 2001). Age differences between the studies may also be responsible for this variation, but no firm evidence exists (Hunt et al. 1989, Vinck et al. 2001). In heritability estimations based on twins, it is assumed that environmental factors are independent of genetic relatedness. It has been suggested that monozygotic twins may share environments to a greater degree than do dizygotic twins, which may result in a closer blood pressure correlation between monozygotic twins, and thus an overestimation of genetic effects (Harrap 1994). Most studies do, however, support the equal environments assumption, i.e., that MZ and DZ twins share environments equally (Kendler et al. 1993, Maes et al. 1997, Kendler and Gardner 1998).

Genes

The argument whether hypertension is caused by one major gene or by the sum of a large number of genes involved in the determination of blood pressure began more than half a century ago. Platt (1947) proposed a major gene effect, while Pickering (1959) argued that blood pressure is a multigenic trait. Today, the consensus is that blood pressure is not inherited as a dichotomous categorization as hypertension and normotension, but as a continuous characteristic with familial factors operating at all levels of blood pressure (Harrap 1994, Luft 1998, Rutherford 2003). In all likelihood, the number of genes affecting blood pressure, and thus predisposing to hypertension, is large, and the effect of single genes is small (Luft 1998). There exist, however, rare monogenic forms of hypertension, for example, the glucocorticoid-remediable aldosteronism caused by a chimeric 11 β-hydroxylase/aldosterone synthase gene (Lifton et al. 1992) and Liddle's syndrome, with a mutation in either the β- or the γ-subunit of an epithelial sodium-channel gene (ENaC) (Shimkets et al. 1994, Hansson et al. 1995). These are autosomal dominant monogenic forms of human hypertension, whereas apparent mineralocorticoid excess can occur as an autosomal recessive disorder resulting from a mutated gene for 11 β-hydroxysteroid dehydrogenase (Mune et al. 1995). All identified monogenic forms of hypertension are results of mutated gene products acting in the kidney, altering net renal salt reabsorbation (Lifton et al. 2001)

The genes of the renin-angiotensin system have been widely studied in relation to hypertension (Smithies et al. 2000). Some examples of suggestive findings are as follows. Evidence exists for association and genetic linkage of the DD genotype of the angiotensin-converting enzyme (ACE) gene with hypertension and blood pressure in men but not in women (O'Donnell et al. 1998, Fornage et al. 1998, Stankovic et al. 2002). A variant of the angiotensinogen gene, the M235T polymorphism, is, in some studies, associated with hypertension (Jeunemaitre et al. 1992, Staessen et al. 1999). The CC genotype of the angiotensin II type 1 receptor gene polymorphisms seems to be linked to hypertension, as well (Bonnardeaux et al. 1994, Hindorff et al. 2002, Stankovic et al. 2003). Polymorphisms in the β$_2$-adrenergic receptor (Timmermann et al. 1998, Castellano et al. 2003) and in the G-protein β$_3$-subunit (Siffert et al. 1998) genes have also been associated with hypertension, and α-adducin polymorphisms

with sodium sensitivity in hypertensives (Manunta et al. 1998). In recent years, genome-wide linkage scans have provided several suggestive linkages for hypertension that promise significant progress in knowledge of the genetic basis of hypertension (Samani 2003). However, despite the many published linkage studies, very few have been followed up with attempts to perform linkage disequilibrium mapping, positional cloning, or candidate gene association studies (Melander 2002).

The fact that for most candidate genes, including the aforementioned genes, a lot of negative findings also exist, suggests that these single genes have, at most, very modest effects on blood pressure. This lack of reproducibility is an indication of the difficulties in genetic investigation of multifactorial traits. (Lifton et al. 2001)

Furthermore, because of a complicated network of feedback mechanisms, gene-gene and gene-environment interactions may result in the same gene variant's having an opposite effect on blood pressure in different environments. This puts very high demands, not entirely met today, on statistical methods in the search for candidate genes for hypertension (Barlassina et al. 2002). For example, polymorphisms in the α-adducin and aldosterone synthase genes significantly affect the influence of DD, ID, and II ACE genotypes on blood pressure. In one study (Barlassina et al. 2000), the ACE genotypes did not influence blood pressure per se, but when α-adducin polymorphisms were taken into account, D alleles were associated with increase in blood pressure response to sodium infusion. Moreover, the increased incidence of hypertension with the ACE DD genotype, compared with ID and II, was, when α-adducin and aldosterone synthase polymorphisms were taken into account, magnified from +31% to +250% (Staessen et al. 2001), whereas α-adducin and aldosterone synthase polymorphisms had little effect on risk for hypertension per se in that study.

Muscle fibre type
Muscle fibre-type proportion is mostly determined by genetic factors (Simoneau and Bouchard 1995). The percentage of type I muscle fibres and blood pressure are inversely correlated, and hypertensives have a lower type I fibre proportion than do normotensives (Juhlin-Dannfelt et al. 1979, Frisk-Holmberg et al. 1983). Both these reports found a correlation between mean arterial pressure and fibre-type distribution when examining hypertensives and normotensives separately. The results for the groups combined were, however, not reported. Correspondingly, Hedman et al. (2000) reported no correlation between blood pressure and fibre-type distribution in the whole study group, but in the hypertensive group alone, the proportions of type I and type II fibres were significantly related to mean arterial pressure. This result persisted also after controlling for obesity and physical activity. Muscle fibre proportion did not differ between hypertensives and normotensives in that study, nor in another study (Toft et al. 1999) that did not, however, examine the association between blood pressure measurements and fibre type. Krotkiewski et al. (1998) investigated obese women and found a strong inverse correlation between percentage of type I fibres and systolic and diastolic blood pressure.

Type I fibre proportion is negatively correlated with vascular resistance in the leg (Juhlin-Dannfelt et al. 1979) and positively correlated with leg blood flow during exercise (Frisk-Holmberg et al. 1981). This may in part be the result of the fact that the number of capillaries surrounding type I fibres is higher than around type II fibres

(Andersen 1975, Krotkiewski et al. 1998). Whether this association is independent of leisure time physical activity is, however, unknown. Moreover, hypertensives have a lower capillary density than do normotensives (Henrich et al. 1988, Hedman et al. 2000), and the increase in blood pressure from 50 to 70 years of age is strongly inversely associated with capillary density (Hedman et al. 2000).

2.2.5. Hypertension as a risk factor

Hypertension shortens life-expectancy (Tsevat et al. 1991, Kiiskinen et al. 1998). Life-expectancy was 2.7 years shorter among men with diastolic blood pressure >104 mmHg than among men with diastolic pressure <95 mmHg. Of this, 2.0 years was due to cardiovascular mortality alone. In women, the differences were a respective 2.0 and 1.5 years (Kiiskinen et al. 1998). All-cause, cardiovascular, and especially coronary heart disease, but not stroke, mortality rates are constantly higher with increased pulse pressure across all levels of mean blood pressure and all age groups (Benetos et al. 1997). Of all atherosclerotic cardiovascular events, 35% may be attributable to hypertension (Kannel 1996). In recent years, it appears that systolic blood pressure is even more important as a predictor of risk for cardiovascular events than is diastolic pressure (Kannel 2000).

Hypertension is the most important risk factor for stroke (Collins et al. 1990, MacMahon et al. 1990). A difference of 6 mmHg in diastolic blood pressure is associated with a 36% difference in the risk for stroke (MacMahon 1989). Most of the strokes in the hypertensive are atherosclerotic brain infarctions; and with increased severity of hypertension, the proportion of strokes due to brain infarction increases along with a decrease in the proportion due to subarachnoid haemorrhage and cerebral emboli, but the proportion due to intracerebral haemorrhage is unchanged (Kannel 1996).

High systolic and high diastolic blood pressures, as well as high pulse pressure, are risk factors for coronary heart disease (Franklin et al. 1999, Domanski et al. 2001). When analysed together, systolic blood pressure and pulse pressure positively associated with coronary heart disease risk, whereas diastolic pressure negatively associated with risk at any level of systolic pressure above 120 mmHg (Franklin et al. 1999). Furthermore, hypertensive men have a 2-fold and women a 3-fold risk for developing congestive heart failure in 14 years compared with risks in normotensives, and hypertension accounts for 39% of heart failure cases in men and for 59% in women (Levy et al. 1996).

Left ventricular hypertrophy occurs in 23 to 56% of hypertensives, whereas the occurrence among normotensives is less than 10% (Devereux 1987, Devereux et al. 1987). An increase of 20 mmHg in blood pressure elevates risk for left ventricular hypertrophy by 43% in men and 25% in women (Levy et al. 1988).

Hypertension causes renal disease; in Europe, the proportion of end-stage renal disease caused by hypertension is 13% (Valderrábano et al. 1998). Systolic blood pressure is an independent predictor of a decline in kidney function (Young et al. 2002).

Interestingly, increases in pulse pressure have recently been associated with an elevated C-reactive protein level (Abramson et al. 2002) known to be a marker of future risk for coronary heart disease and myocardial infarction (Koenig et al. 1999, Ridker et al. 2000, Ridker 2001).

In developed countries, one of the leading causes of visual impairment is hypertension (Hurcomb et al. 2001). Hypertensive retinopathy is the second most common retinal vascular disease after diabetic retinopathy (Marshall and Malinovsky 1998). The prevalence of retinopathy in the over-40 non-diabetic population was 11% in hypertensives and 6% in normotensives (Klein et al. 1993)

A decrease in high blood pressure by medication reduces strokes by 38% and severe coronary events by 16% in 5 years (Collins and MacMahon 1994). Medication for isolated systolic hypertension reduces strokes by 30% and coronary events by 23% in 4 years (Staessen et al. 2000).

3. AIMS OF THE STUDY

The main aim of the present study was to investigate the nature of the association between leisure-time physical activity and occurrence of hypertension in athletes and in population-based, genetically informative cohorts of adult men and women in prospective and cross-sectional studies.

Specifically, the following hypotheses were tested:

1. Long-term very vigorous exercise in adulthood is associated with reduced future risk for hypertension in middle-aged and older men.

2. Longitudinal changes in physical activity levels are associated with occurrence of hypertension.

3. The genetic components of blood pressure and physical activity are correlated.

4. A high proportion of type I muscle fibres predicts low blood pressure levels and accounts for the association between physical activity and low blood pressure levels.

4. MATERIALS AND METHODS

Please refer to the original articles (I-V) and references for a more detailed description of the studies. Designs of the studies are summarized in Table 6.

Table 6 Summary of designs of studies. Subjects were male unless otherwise stated.

Study	Population	Design	Number of subjects	Baseline	Follow-up	Main outcome measure / Definition of incident cases
I	Athletes	Follow-up	264	Ranking list in 1984	Questionnaire in 1995	Prevalence of hypertension
	Controls		388	Questionnaire and register data in 1985	Questionnaire in 1995	Prevalence of hypertension
II	Athletes and controls	Follow-up	569 athletes 319 controls	Questionnaire and register data in 1985	Questionnaire in 1995	Incident cases: hypertensive in 1995 but not in 1985
III	Twins (no twin data analyses)	Follow-up	3 931 men 4 381 women	Questionnaires in 1975 and 1981	Questionnaire in 1990	Incident cases: hypertensive in 1990 but not in 1981
IV	Twins	Cross-sectional	71 MZ pairs 104 DZ pairs	Interview on lifetime physical activity	Measurement in 1997-1999	Blood pressure
V	Healthy men	Follow-up	64	Muscle fibre-type proportion in 1984	Measurement in 2003	Blood pressure

4.1. Study populations

Subjects in these studies originated from several sources; male top-level master orienteering runners (I), male athletes who represented Finland between 1920 and 1965 in international competitions (II), controls, of similar ages as the athletes, selected from among Finnish men who at age 20 were healthy (I, II), the Finnish Twin Cohort (III, IV), and middle-aged men recruited from private companies in Helsinki and its surroundings (V).

4.1.1. Master orienteers (I)

Top-level master orienteering runners were chosen to represent subjects engaged in long-term vigorous exercise. Orienteers typically carry on competing as masters (35 years and upwards). In Finland, master orienteers are ranked by competition results, and a high position in the ranking list is an indicator of years of intense endurance training. This consists mostly of running, often over rough terrain, and cross-country skiing during winter. The 60 top-ranked orienteers in each of the five classes: men aged 35 to 39 years, 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 59 years from the 1984 ranking list, were enrolled. These 300 orienteers represented 10% of all currently ranked orienteers in these classes.

A questionnaire was posted to the orienteers in 1995. Eight (2.7%) orienteers could not be contacted because of death or unknown address. The questionnaire was thus posted to 292 men, and 264 (90.4%) responded.

4.1.2. Former elite athletes (II)

Male athletes who represented Finland between 1920 and 1965 at least once in the Olympic Games, world or European championships, or other international competitions (athletic contests between 2 or 3 countries) were identified via multiple sources (Sarna et al. 1993). The full name, birthplace, and date of birth were traced for 98% of the athletes from selected sports. The original cohort of athletes comprised 2 448 men.

A questionnaire was posted to the athletes in 1985 and in 1995. Those who could not be contacted because of death or unknown address, or who did not respond to both of these questionnaires (n=1 617) were excluded. Response rates for the athletes contacted were 80 to 90% by sport in 1985 and 83% in 1995. Those aged over 65 in 1985 were also excluded. Further, those classified as hypertensive (see below) in 1985 (n=144; 17%) were excluded. The final sample comprised 569 athletes.

The sports were grouped according to type of training needed to achieve maximal result, i.e., endurance sports and mixed sports (mixed sports including mostly team sports) (n=386) and power sports (n=183). The endurance and mixed sports were combined into one group in order to gain sufficient statistical power for the study.

4.1.3. Controls (I, II)

Controls were selected among Finnish men who at age 20 had been classified as completely healthy (military class AI, fully fit for ordinary military service) at the medical examination preceding their conscription. They were drawn from the public register archives of men eligible for military service and matched for birth cohort and area of residence with the athletes (Sarna et al. 1993). The original cohort of controls comprised 1 712 men.

4.1.3.1. Special aspects of selection criteria for controls in Study I

The control sample comprised all 495 men from the control cohort, aged 35 to 59 in 1984. These controls had responded in 1985 to a questionnaire on health and lifestyle. In 1985, data on diseases were also collected from the Finnish registers for hospital inpatient discharges, for reimbursable medications, and for disability pensions (Kujala et al. 1994). In 1995, another questionnaire was posted to all controls except for 46 (8.6%) who could not be contacted because of death or unknown address, and 425 (94.7%) responded. Men who had ischemic heart disease in 1985 on the basis of register data or the questionnaire (n=37, 8.7%) were excluded from the control group. This exclusion was based on the assumption that among the orienteers, overt ischemic heart disease was highly improbable when they were highly ranked. After this exclusion, 388 men remained in the control group.

4.1.3.2. Special aspects of selection criteria for controls in Study II

Of the controls from the original cohort, 1 212 men were excluded because of death or unknown address, or failure to respond to both questionnaires (in 1985 and in 1995). Response rates were 77% in 1985 and 81% in 1995. Those who were under 65 in 1985 were included. Those 127 men (25%) who were hypertensive in 1985 (see below) were excluded. The final sample comprised 319 controls.

4.1.4. The Finnish Twin Cohort (III, IV)

The Finnish Twin Cohort comprises samples of Finnish twin pairs. The oldest cohort, used in this project, comprises all same-sex twin pairs born in Finland before 1958 with both co-twins alive in 1967 (Kaprio et al. 1978, Kaprio and Koskenvuo 2002). Subjects were posted a questionnaire in 1975 and in 1981. The response rate in 1975 among those whose address could be identified (93.5% of subjects) was 87.6%. The re-response rate in 1981 among those responding in 1975 and still alive in 1981 was 90.7%.

4.1.4.1. Special aspects of selection criteria for twins in Study III

The target group consisted of cohort subjects who provided complete questionnaire data on the intensity of their leisure physical activity in 1975 and in 1981, and were aged 24 to 51 on January 1, 1982. Of these 19 908 subjects, those 17 968 who were at work (including women working at home and students) in 1981 were included, as those disabled for work may also be unable to exercise. Because chronic disease may restrict the ability to exercise or because persons with disease may be advised to change their physical activity patterns, those 2 064 cohort members who had chronic disease, that is ischemic heart disease, myocardial infarction, diabetes, chronic obstructive pulmonary diseases, or malignant cancer, prior to January 1, 1983, were excluded, as described elsewhere (Kujala et al. 1998, 2002). Both questionnaire data and register-based information from the nationwide hospital discharge register (Keskimäki et al. 1991) and the register for reimbursable medication of the National Social Insurance Institution (Kujala et al. 1994) were used for the exclusion. In the study cohort there were thus 15 904 subjects (7 811 men and 8 093 women) healthy at baseline, before hypertensive status was considered. In 1990, a questionnaire was posted to all members of twin pairs in the study cohort fulfilling the aforementioned criteria and born between 1930 and 1957 with both members known to be alive, non-institutionalized, and living in Finland at a known address (n=11 724). If one co-twin was missing from the cohort, the questionnaire was not posted to the other co-twin. The individual response rate was 82.8%, and the number of subjects responding 9 704 (4 504 men and 5 200 women).

Because incident hypertension was studied, those 868 (8.9%) subjects, 398 (8.8%) men and 470 (9.0%) women classified as hypertensive at baseline in 1981 (see below) were excluded. Then those 489 (5.5%) subjects who provided incomplete questionnaire data on hypertension risk factors were excluded. After this exclusion 8 347 subjects (3 944 men and 4 403 women) remained in the study cohort. Finally, those subjects for whom data of hypertensive status in 1990 were unobtainable were excluded.

The final cohort consisted of 8 312 subjects, 3 931 men and 4 381 women who had provided risk factor data and who were healthy and non-hypertensive at baseline (1981), and had provided data on hypertensive status in 1990.

4.1.4.2. Special aspects of selection criteria for twins in Study IV

The subjects were male twins from the Finnish Twin Cohort (Kaprio et al. 1978, Kaprio and Koskenvuo 2002): 117 monozygotic (MZ) and 120 dizygotic (DZ) twin pairs selected by consistent discordances in occupational physical loading, exercise and sports activity, vehicular driving, or smoking, according to data from the two questionnaires (in 1975 an in 1981) (Battié et al. 1995a). The exposures were originally selected to study the main suspected risk factors for spinal disorders in the Twin Spine Study (Battié et al. 1995a). Added to the sample were 30 MZ and 33 DZ pairs chosen at random from the pool of remaining pairs.

Of the entire sample, 99 MZ and 142 DZ pairs underwent examinations and blood pressure measurements between 1997 and 1999. Those pairs in which at least one of the co-twins had diabetes (3 concordant and 3 discordant MZ pairs, 11 discordant DZ pairs) or used medication for hypertension or other cardiovascular medication influencing blood pressure (14 concordant and 14 discordant MZ pairs, 11 concordant, 18 discordant DZ pairs) were excluded from those analyses having blood pressure as the dependent variable. Many of these subjects had both these conditions. Thus there remained 71 MZ pairs and 104 DZ pairs. The mean age of the subjects was 52.0 (range 40-72) for the MZ pairs and 49.3 (range 40-70) for the DZ pairs (Table 7).

A total of 191 MZ subjects and 293 DZ subjects, including those with diabetes or antihypertensive medication, were analysed in regard to incident hypertension. These were all in whom blood pressure was measured, plus 12 DZ subjects in whom blood pressure was not measured but who were classified as hypertensive based on medication (these 12 were excluded when prevalence of hypertension was analysed). The 17 subjects who did not report having hypertension but did use medication that influences blood pressure were excluded. The mean age of the men in these analyses was 51.8.

4.1.5. Middle-aged men (V)

In 1984, 79 apparently healthy men without medications participated in the baseline examinations (Tikkanen et al. 1991, 1998). At follow-up in late 2002, an invitation to a new set of measurements went to 74 subjects; four had died, and one had moved abroad. Of these 74, 65 (87.8%) participated in examinations in 2003. One had suffered intracerebral haemorrhagia 10 years earlier in an accident causing permanent limitation of daily physical activity and was therefore excluded from all analyses.

Table 7 Subject characteristics.

Study	Population	Number of subjects	Mean age at assessment (range)	Time of assessment (baseline)
I	Athletes	264	49.6 (39-60)	1984
	Controls	388	58.5 (36-60)	
II	Athletes			1985
	Mixed	386	50.8 (36-65)	
	Power	183	51.7 (38-65)	
	Controls	319	49.5 (38-65)	
III	Twins			1981
	Men	3 931	34.6 (24-51)	
	Women	4 381	34.1 (24-51)	
IV	Twins	350	50.4 (40-72)	1997-1999
V	Men	64	40.2 (32-58)	1984

4.2. Collection of data

4.2.1. Questionnaires (I-V)

The questionnaires posted to the subjects were, for the most part, similar and included items on physical attributes, sociodemographic factors, smoking status and use of alcohol, physical activity and sporting background, use of medications, and occurrence of selected diseases verified by physicians.

4.2.2. Register data (I-III)

Data on diseases also came from the Finnish registers for hospital inpatient discharges, reimbursable medications, and disability pensions (Kujala et al. 1994) (I, III), or from only the register for reimbursable medications (II).

4.2.3. Measurements and interviews (II, IV, V)

The blood pressure of a subgroup of the athletes in Study II (n=56) (Kujala et al. 1995) was measured (sphygmomanometrically in a sitting position after 15 minutes' rest).

Blood pressure measurements in Study IV were performed according to a standard protocol. After a 2-minute supine rest, continuous beat-to-beat arterial blood pressure from the middle finger was recorded (Finapres™ Blood Pressure Monitor, Ohmeda, Inc., Englewood, CO, USA) for 5 minutes during supine rest, with the finger with the cuff immobile at heart level. Mean 5-minute systolic and diastolic arterial pressures were calculated. The Finapres finger blood pressure recording system measurements

correspond well with intra-arterial brachial and radial measurements at rest (Imholz et al. 1988, Parati et al. 1989, Imholz et al. 1990, Bos et al. 1995).

In Study V, blood pressure was measured in the morning by the same person, a trained nurse, using a standard mercury manometer. After a 5-minute rest, the measurements were made from the right arm, with the subjects sitting in a quiet room. Korotkoff phase I and phase V were used for systolic and diastolic blood pressure respectively. Two measurements were made for each subject, and the lower one (lower mean arterial pressure) recorded.

In Study V, in 1984, muscle fibre distribution (percentage of type I fibres, type I%) was analysed from samples taken from the lateral portion of the quadriceps femoris muscle by needle biopsy (Tikkanen et al. 1991). The muscle samples were stained for actomyosin ATPase by preincubation at pH 4.3 (Guth and Samaha 1970). This staining clearly separates the two main fibre types, type I and type II fibres, respectively stained dark and remaining unstained (Saltin and Gollnick 1983).

Subjects' height and weight were measured (IV, V). The detailed, structured interview conducted with each subject covered exercise, alcohol consumption, and chronic diseases and use of medication (IV, V). In Study IV, occupational physical activities and smoking history were also assessed by interview.

4.3. Definition of hypertension

4.3.1. Definition of hypertension at baseline (II, III)

In the 1981 questionnaire, the twins were asked the following: 'Has a physician ever told you that your blood pressure is or has been elevated?' and 'Has a nurse or a physician measured your blood pressure during the last 5 years?' Subjects who responded yes to the first question were classified as hypertensive in 1981. The latter question had several response alternatives: '1) No, 2) I do not remember, 3) It was normal, 4) It was mildly elevated, but no medication was prescribed, 5) It was elevated, medication was prescribed, but this treatment has now ended, and 6) It was elevated and the medication prescribed is still continuing'. Subjects who chose number 6 were classified as hypertensive in 1981. The subjects also reported the number of days they had used medication for hypertension during the previous year. Alternatives were '1) None, 2) less than 10 days, 3) 10 to 59 days, 4) 60 to 180 days (2 to 6 months), and 5) more than 180 days (more than 6 months)'. Those who used medication for 10 or more days were classified as hypertensive in 1981. Subjects granted reimbursable medication for hypertension before January 1, 1983, based on medical certificate data from the Social Insurance Institution of Finland (Kujala et al. 1994), were also so classified (III).

Athletes and controls who at baseline in the 1985 questionnaire reported that a physician had told them their blood pressure was or had been elevated or who reported having used medication for hypertension were classified as hypertensive in 1985. Those granted the right to reimbursable medication for hypertension in 1985 or earlier according to the register for reimbursable medications (Kujala et al. 1994) were also classified as hypertensive (II).

4.3.2. Definition of hypertension at endpoint (I-IV)

The twins who in the 1990 questionnaire reported physician-diagnosed hypertension or who reported that they had used medication for hypertension on 60 or more days during the previous year were classified as hypertensive in 1990 (III).

In the 1995 questionnaire, the master orienteers and controls answered the following questions: 'Have you ever used medication for hypertension?', 'Has your blood pressure always been normal?', and 'Has a doctor or a nurse ever said that your blood pressure is elevated?' These definitions separately served as endpoints (I).

Former athletes and controls who in the 1995 questionnaire reported having used medication for hypertension or who, according to the register, had been granted reimbursable medication for hypertension between 1986 and 1995 were classified as hypertensive in 1995 (II).

In Study IV, hypertension was defined as use of medication for hypertension or a systolic blood pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg in the measurements (IV).

4.3.3. Validity of classifications of hypertension (I-III)

To assess the validity of the classification of hypertension in Studies I and II, blood pressure measurements were compared with questionnaire responses. The blood pressure of a subgroup of the athletes in Study II (n=56) had been measured in 1992. The measurements were compared between those who were classified as hypertensive in 1995 and those classified as healthy. Though only an indirect measure, this comparison supports the validity of the classification, because those classified as healthy at baseline in 1985 had lower systolic (mean (standard deviation, SD) 139 (17) vs. 150 (21) mmHg; p=0.049 by t-test) and diastolic (87 (9) vs. 98 (13) mmHg; p=0.0005) blood pressure levels in 1992 (II).

For validation analyses of the classification of hypertension in Study III, questionnaire data were compared with blood pressure. Blood pressure was measured between 1993 and 1995 in a subgroup of the study subjects in the present study (Kaprio et al. 2001), between 1993 and 1995. Two measurements were made, and mean systolic and diastolic blood pressures computed for each subject. Systolic pressure was available for 225 subjects and diastolic pressure for 224. Those using medication for hypertension at that time were not excluded. The validity of the classification of hypertension was assessed by t-test by comparing blood pressure measurements between those classified as hypertensive according to the 1990 questionnaire and those classified as healthy. Again, though only an indirect measure, the comparison supports the validity of the classification. Those classified as hypertensive according to the questionnaire in 1990, 28 (12.4%) for systolic and 27 (12.1%) for diastolic pressure, had higher systolic: mean (SD) being 142 (17) vs. 130 (16) mmHg, p=0.0002 and higher diastolic: 86 (10) vs. 80 (9) mmHg, p=0.0009 blood pressure than did those reporting normal blood pressure values (III).

4.4. Assessment of risk factors

4.4.1. Assessment of physical activity (I-V)

Assessment of volume of physical activity was based in the questionnaires on a series of structured questions (Kaprio et al. 1978, Kujala et al. 1998) on leisure physical activity (monthly frequency, mean duration, and mean intensity of physical activity sessions). The activity metabolic index was calculated by assigning a multiple of the resting metabolic rate (MET score) to each activity and calculating the product of intensity × duration × frequency of activity (Wilson et al. 1986). This calculation used the following MET values (metabolic equivalents, calculated as work metabolic rate divided by resting metabolic rate): 1) 4 corresponds to exercise intensity corresponding to walking, 2) 6 to vigorous walking to jogging, 3) 10 to jogging, and 4) 13 to running (I-III).

In study III, volume of physical activity was dichotomized so that those subjects whose volume of activity was ≥2 MET hours per day (corresponding to at least 30 min walking per day) were classified as physically active at leisure. Participation in vigorous physical activity was also assessed, based on the following question: 'Is your physical activity during leisure time about as strenuous on average as: 1) walking, 2) alternately walking and running, 3) jogging, 4) running?' Those who chose alternative 3 or 4 were classified as participating in vigorous activity (III).

Study IV determined by interview lifetime history of leisure-time physical activity. Physical activity was classified as aerobic exercise, power sports, and other sports. Aerobic exercise was classified under regular exercise and intensity of exercise. Three time-periods of regular exercise were examined separately: entire lifetime, past year, and adolescence (ages 12-20). The intensity of aerobic exercise was analysed for the entire lifetime and for the past year separately. The intensity of each aerobic exercise the subjects engaged in they classified themselves as 1) light, 2) medium, or 3) heavy. The number of observations was too small for sufficient power for examining intensity of aerobic exercise in adolescence separately. Power sports and other sports were examined for entire lifetime, past year, and adolescence separately (IV).

In Study V, personal interviews were conducted in 1984 at baseline, and in 2003 at follow-up. In 1984, total leisure-time physical activity was calculated by multiplying activity (in METs) by duration and frequency of activity and was expressed as MET hours per week (Tikkanen et al. 1998). In 2003, physical activity was assessed by the Kuopio Ischemic Heart Disease Study 12-month physical activity questionnaire (Salonen and Lakka 1987, Lakka and Salonen 1997), which was self-administered by the subjects. A subsequent interview ensured completeness, and all interviews were conducted by the same person. The questionnaire included a list of activities for which the subjects reported mean intensity, duration, and frequency for each month. The MET of the different intensities for each type of activity was categorized (Lakka and Salonen 1997). Volume of physical activity was expressed in MET hours per week. Both total physical activity volume and volume of exercise (activity such as household activity excluded) were calculated (V).

4.4.2. Assessment of potential confounding factors (I-V)

Body mass index (BMI), use of alcohol (I-V), smoking (I-IV), occupational group (II), work-related physical activity (III, IV), chronic diseases (IV), and use of medication (IV, V) were treated as potential confounding factors.

BMI was calculated from the height and weight of the subjects (weight/height^2), which were self-reported (I-III) or measured (IV, V). In Study III, this variable was dichotomized, and those whose BMI was $\geq$27 kg/m^2 were classified as overweight.

Smoking status was classified according to the responses to a detailed smoking history (Kaprio et al. 1981). Non-smokers were those who reported that they had never smoked more than a total of 5 to 10 packs of cigarettes. All subjects who had quit smoking were classified as former smokers. Those few smokers who had never smoked daily or almost daily were classified as former smokers for the purpose of the analyses. Other subjects were classified as current smokers (I, II). Study III used a dichotomized classification; only current smokers were classified as smokers. In Study IV, smoking exposure was calculated as pack-years (Battié et al. 1995a).

Use of alcohol was recorded in beverage-type specific items for frequency and quantity, and then converted into grams of absolute alcohol per day (I, II) or per week (IV, V) (Kaprio et al. 1987). In Study III, those who consumed more than the equivalent of a bottle of wine at least once a month on a single occasion were classified as heavy users of alcohol (Kaprio et al. 1987).

Occupational data were collected in part from the central population registry of Finland and in part from the 1985 questionnaire. Classification by occupational group was into the following categories: executives, clerical staff, skilled workers, unskilled workers, and farmers. Each person was classified according to the occupation he held for the longest period of his life (Sarna et al. 1993) (II).

Work-related physical activity was classified as sedentary or non-sedentary in Study III. In Study IV, every job held for at least 3 months during each subject's lifetime work history was discussed and noted in detail (Battié 1995a), with an activity index then calculated.

History of chronic diseases (IV) *and use of medication* (IV, V) were also noted.

4.5. Ethical aspects

All studies have been approved by the appropriate ethics committees.

4.6. Statistical methods

4.6.1. General

BMDP Statistical software, Berkeley, CA, USA (I, II), and STATA software, release 6.0, Stata Corporation, College Station, TX, USA (III, IV), were used for logistic

regression analyses of the data, and SPSS for Windows, version 11.0.1, SPSS Inc., IL, USA, for regression analyses (V). All significance tests were two-tailed.

4.6.2. Individual-based analyses (I-V)

Logistic regression analyses were used to assess the associations of different physical activity measures and confounding factors with risk for hypertension. Analyses were made first with models including only physical activity variables and age, and then with different confounding factors included to assess the independent associations of physical activity and risk for hypertension (I-III).

When the outcome measure was blood pressure as a continuous variable, multiple regression analyses were used to investigate how physical activity measures, or muscle fibre-type distribution, associated with systolic and diastolic blood pressure. In these analyses as well, confounding factors were included in the models after initial assessment of associations adjusted only for age (IV, V).

4.6.3. Pairwise analyses in twins (IV)

Standard univariate twin analyses (Williams et al. 1992, Posthuma et al. 2003) were carried out to estimate genetic and environmental components of variance for blood pressure using maximum likelihood based on sample covariance matrices and means (Neale et al. 1992, Posthuma et al. 2003). Under the study design of twins reared together, it is possible to model four separate parameters: an additive genetic (A) component, effects due to dominance (D), and shared (C) and non-shared (E) environmental components. Additive genetic effects (A) signify that the effect of one allele is added to the effect of another allele, and dominant effects (D) genetic effects other than additive. Heritability is an estimate of the proportional contribution of additive genetic effects on the phenotypic variation in a trait (Posthuma et al. 2003). Shared environment (C) signifies environmental factors that are similar for both co-twins, and non-shared environment (E) environmental factors that the co-twins do not share, also including measurement error (Posthuma et al. 2003).

Using this design of twins reared together, one can fit models based on some combinations of these parameters: AE, ACE, ADE, CE, and E (Neale et al. 1992, Posthuma et al. 2003). Specific independent variables and age were added as regressors to the blood pressure models to evaluate how much variance each specific variable accounted for and how much of the remaining variance was then accounted for by age, genetic, and environmental components.

A bivariate twin analysis with age-correction revealed whether genetic and environmental effects on physical activity are correlated with genetic and environmental effects on blood pressure (r_g and r_e respectively). This analysis was carried out with bivariate Cholesky decomposition parametrization (Neale et al. 1992, Posthuma et al. 2003). The structural models were estimated with the Mx program (Neale 1999).

5. RESULTS

5.1. Risk factors for hypertension (I-V)

The master endurance athletes (I) were, as expected, the most physically active population. Their mean MET hours per week were 77.6, corresponding to almost 8 hours of jogging or about 6 hours of running per week. The former elite athletes (II) were exercising more than the controls (II). The twins (III) were at about 30 years of age exercising as much as the 50-year-old former athletes (II), corresponding to about 3 to 3.5 hours of jogging per week. The middle-aged men (V) took exercise corresponding to about 3 hours of jogging per week. The endurance athletes had lower BMI, and smoked less often than did controls (I, II) (Table 8).

Table 8 Means and proportions for physical activity and potential confounding factors for subjects

Study	Population	Age in years (range)	MET hours/week (SD, range)	BMI kg/m^2 (SD, range)	Alcohol-use g/day (SD, range)	Non-smokers	Former smokers	Current smokers
I	Athletes	60.6	77.6	23.2	9.9	73%	24%	3%
	(n=264)	(50-71)	(47.3, 1.5-227.5)	(1.7, 18.7-31.1)	(11.4, 0-72)			
	Controls	58.5	18.8	26.8	16.6	31%	46%	23%
	(n=388)	(47-71)	(22.4, 0-146.3)	(3.5, 16.2-42.6)	(21.0, 0-161)			
II	Athletes							
	Mixed	50.8	34.8	25.1	14.2	52%	35%	13%
	(n=386)	(36-65)	(35.3, 0-175.0)	(2.5, 19.2-40.1)	(16.2, 0-145)			
	Power	51.7	30.7	27.3	11.6	55%	30%	15%
	(n=183)	(38-65)	(34.9, 0-227.5)	(3.2, 19.7-38.1)	(15.7, 0-117)			
	Controls	49.5	16.1	25.9	13.3	29%	42%	30%
	(n=319)	(38-65)	(26.3, 0-227.5)	(3.0, 18.3-38.8)	(17.7, 0-143)			
III	Twins							
	Men	28.6	21.4	23.2	11.8	38%	24%	38%
	(n=3 931)	(18-45)	(26.2, 0-224.6)	(2.7, 15.6-34.7)	(14.2, 0-181)			
	Women	28.1	16.8	21.4	4.4	60%	15%	26%
	(n=4 381)	(18-45)	(18.3, 0-210.6)	(2.7, 14.5-43.0)	(6.6, 0-118)			
	Twins							
	Men	34.6	22.9	24.0	12.1	37%	29%	34%
	(n=3 931)	(24-51)	(27.0, 0-224.6)	(2.7, 16.4-36.3)	(14.3, 0-129)			
	Women	34.1	19.0	22.1	4.3	59%	19%	21%
	(n=4 381)	(24-51)	(18.6, 0-224.6)	(13.6-48.2)	(6.4, 0-114.8)			
IV	Twins	50.4	Not available	25.4	10.5	34%	38%	28%
	(n=350)	(40-72)		(3.0, 16.3-34.6)	(12.2, 0-125)			
V	Men	59.2	31.0	26.5	18.9	43%	42%	15%
	(n=64)	(51-77)	(22.4, 0.1-99.9)	(4.0, 17.5-36.6)	(16.5, 0-82.7)			

Men were much more often (25%) persistently participating (in 1975 and in 1981) in vigorous activity (classified as physical activity on average as strenuous as jogging or running vs. walking) than were women (6%). Of those exercising vigorously, a much larger percentage of men than of women were engaged in activities the intensities of which corresponded to running instead of jogging, 42.7% of men vs. 16.9% of women in 1975, and 39.1% of men vs. 22.3% of women in 1981 (III).

5.2. Physical activity and hypertension or blood pressure

5.2.1. Occurrence of hypertension (I-IV)

Absolute measures of occurrence (prevalence and incidence) of hypertension cannot be compared between these four present studies, since classifications of hypertension differed from study to study.

Only 8.7% (95% CI, 5.6-12.8) of master endurance athletes reported having used medication for hypertension, compared with 27.8% (95% CI, 23.4-32.3) of controls. The difference was marked also for proportions of subjects told by a physician or a nurse that their blood pressure was elevated: 23.9% (95% CI, 18.7-29.0) of athletes compared with as high as 45.4% (95% CI, 40.4-50.3) of controls (I).

The cumulative incidence of hypertension between 1986 and 1995 was 23.6% (95% CI, 19.3-27.8) among former elite endurance and mixed-sports athletes. For former power-sports athletes, the incidence was 33.3% (95% CI, 26.5-40.2), and for controls 32.0% (95% CI 26.9-37.1). The endurance and mixed sports group had a significantly lower incidence than did either the power sports group (p=0.014) or the control group (p=0.013) (II).

In the twin population, younger than the former athletes (Table 8), the cumulative incidence of hypertension from 1982 to 1990 was 10.2% (95% CI, 9.3-11.2) for men and 8.0 (95% CI, 7.2-8.8) for women (p=0.003 for sex difference) (III). In the subsample of the twin population in which blood pressure was measured, the prevalence of hypertension was 38.3% (95% CI, 33.9-42.7) (IV).

5.2.2. Risk for hypertension in different physical activity groups in men (I-IV)

The results of the different studies vary somewhat. Each study has, however, found some association between physical activity and hypertension or blood pressure. Engaging in vigorous activity was associated with low risk for hypertension in all questionnaire-based follow-up studies (I-III). Being a master endurance athlete was strongly associated with low risk for hypertension (I), and having been an elite athlete in endurance or mixed sports in young adulthood was associated with low risk, as well. Furthermore, volume of physical activity (MET index) was associated with lower risk: a 14% decrease per increasing MET quartile (for MET quartiles, see Table 3 in Study II) (II). In Study III, in men, vigorous physical activity was associated with low risk, whereas a high volume of physical activity was not associated with risk for hypertension. Participation in vigorous activity only in 1975, but not in 1981, was associated with reduced risk for hypertension between 1982 and 1990, when compared with persistent non-participation (both in 1975 and in 1981) (Table 9) (III).

In Study IV, which was cross-sectional by design, engagement in other sports (other than aerobic or power type sports) was associated with low prevalence of hypertension. No other physical activity variables were associated with prevalence of hypertension (IV).

Table 9 Adjusted odds ratios (with 95% CIs) for risk for hypertension during follow-up for different physical activity groups compared with reference groups in men.

Study	Group	Reference group	Outcome of study	Odds ratio adjusted for		
				Age	Age, alcohol, smoking	Age, alcohol, smoking, BMI
I	Master endurance athletes	Controls	Use of medication for hypertension	0.26 (0.16-0.43)	0.26 (0.15-0.44)	0.43 (0.24-0.77)
II	Endurance and mixed sports	Controls	Use of medication for hypertension	0.67 (0.48-0.94)	0.71[a] (0.49-1.02)	0.78[b] (0.53-1.14)
	Power sports	Controls		1.11 (0.75-1.64)	1.20[a] (0.80-1.80)	1.06[b] (0.69-1.62)
III	Persistently vigorously physically active (in 1975 and in 1981)	Persistently not vigorously active	Physician diagnosed hypertension	0.69 (0.52-0.90)		0.72 (0.55-0.95)
	Vigorously active in 1975 but not in 1981	Persistently not vigorously active		0.62 (0.44-0.89)		0.64 (0.45-0.91)
	Vigorously active in 1981 but not in 1975	Persistently not vigorously active		0.84 (0.60-1.17)		0.84 (0.60-1.18)
	Persistently high volume of physical activity (in 1975 and in 1981)	Persistently low volume of physical activity		0.95 (0.73-1.22)		1.25 (0.93-1.69)
IV	Engaged in non-endurance, non-power sports	Not engaged in non-endurance, non-power sports	Medication for hypertension or blood pressure >140/90 mmHg	0.60 (0.37-0.98)		0.50[c] (0.29-0.85)

[a]Adjusted also for occupational group. [b]Adjusted also for MET and occupational group. [c]Adjusted also for diabetes, but not for alcohol-use.

5.2.3. Physical activity and blood pressure levels in men (IV, V)

High occupational physical loading during the past year was associated with low systolic blood pressure, while regular participation in aerobic exercise during the past year was actually associated with high systolic blood pressure. Aerobic exercise in adolescence and lifetime aerobic sports intensity were associated with low levels of diastolic blood pressure. All these associations were adjusted for age. The means for systolic and diastolic blood pressures by aerobic exercise intensity categories and aerobic exercise in adolescence categories are presented in Figures 1 and 2 (IV).
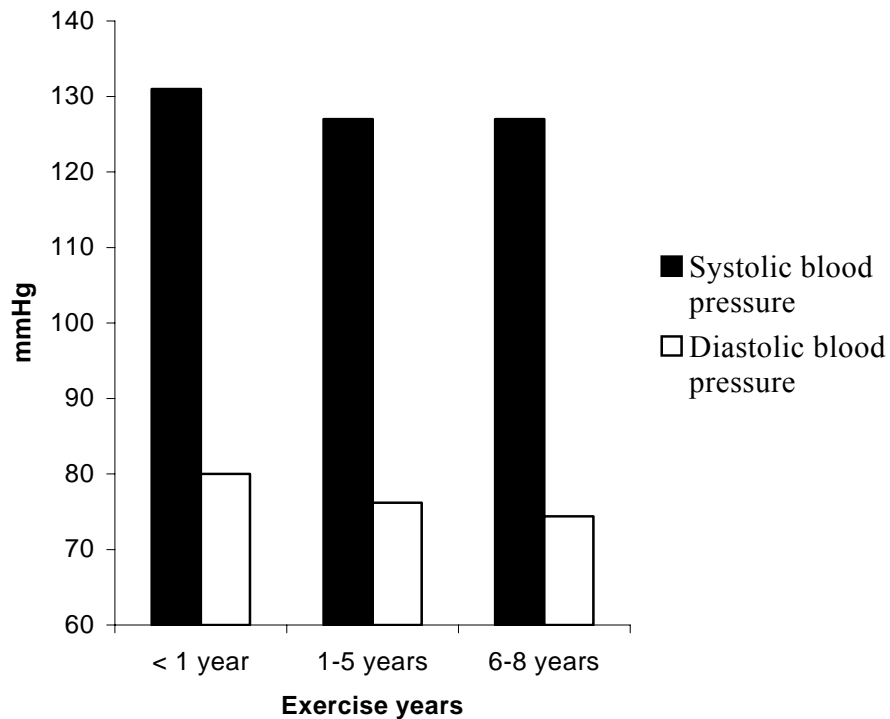
Figure 1 Systolic and diastolic blood pressure means in different exercise categories (number of years of aerobic exercise at least twice per week) for aerobic exercise during adolescence (12-20 years). Differences between groups significant (p<0.05) for diastolic blood pressure.
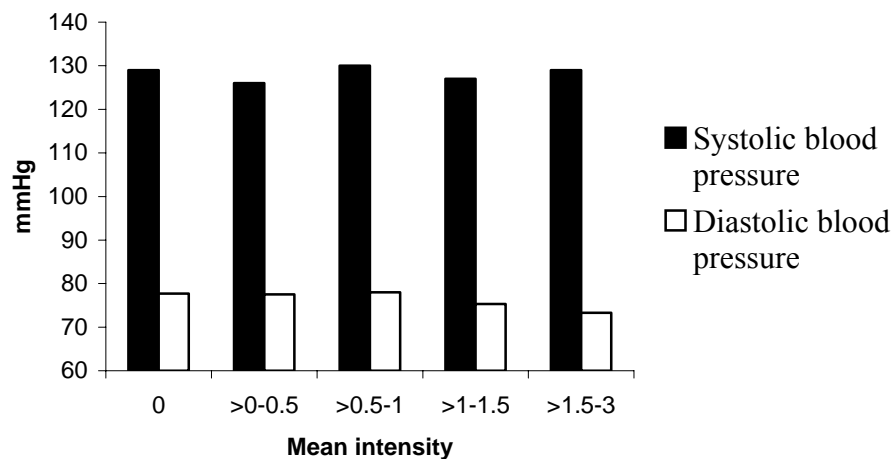
Figure 2 Systolic and diastolic blood pressure means in different aerobic exercise intensity categories (mean intensity during the entire lifetime, self-assessed by subjects, scale 1-3; for details, see section 4.4.1.). The association was significant (p<0.05) for diastolic pressure.

In Study V, high leisure-time physical activity at baseline was associated, adjusted for age and baseline BMI, with low diastolic blood pressure.

5.2.4. Risk for hypertension in different physical activity groups in women (III)

No associations appeared between vigorous physical activity or physical activity volume, and hypertension in women (n=4 381) (III).

5.2.5. Effects of genetic and environmental factors on blood pressure levels (IV, V)

In the univariate twin analysis for both systolic and diastolic blood pressure, the E model, including only the non-shared environment component, could be rejected. All other models (ADE, ACE, AE, and CE, where A is additive genetic effects, D effects due to dominance, C shared environment, and E non-shared environment) fit the data satisfactorily, and were not significantly different from each other. The AE models were the best fitting for univariate analysis for both systolic and diastolic blood pressure (IV).

In the AE model for systolic blood pressure, non-shared environment explained 61% and genetic effects 39% of the variance. The χ^2 of this model was 3.98 with 7 degrees of freedom (df), Akaike's information criterion (AIC; AIC= χ^2-2 × degrees of freedom; lower AIC indicates better fit) was -10.02, and p=0.78. This indicates that the model fits the data well; in this analysis p>0.05 indicates good fit. In the ACE model, non-shared environment still accounted for 61%, and genetics for 39% of the variance in systolic pressure, while common environment had no effect on the variance (IV).

In the AE model, diastolic blood pressure was explained mostly by non-shared environmental effects (64% of the variation), while genetic effects explained 36% (χ^2=4.87, df=7, AIC=-9.13, p=0.68). When the environmental effects shared by both

co-twins were included in the model (ACE), the importance of non-shared environmental effects remained unchanged (65%), but genetic effects accounted for 29% and common environment for 6% of the variance in diastolic pressure. When age and physical activity (specific independent variables) were added as regressors to the AE model, aerobic exercise in adolescence explained 5% of the variation in diastolic blood pressure, while the effect of aerobic exercise intensity during the whole lifetime was not significant in this model (IV).

Mean systolic and diastolic blood pressures were significantly lower among those whose muscle fibre type I percentage (type I%) was ≥50% than among those with a type I% <50% (Figure 3). Type I% was significantly associated with low systolic and low diastolic blood pressure, adjusted for physical activity and BMI in 1984, and for age both when all subjects were included in the analyses and when only those without any antihypertensive medication were included. In the latter case, an increase in type I% by one unit was associated with a 0.58 mmHg (95% CI, 0.11, 1.06; p=0.018) and 0.25 mmHg (95% CI, 0.045, 0.45; p=0.018) decrease respectively in systolic and diastolic blood pressure. Type I% was the only significant predictor of both systolic and diastolic blood pressure. Adding use of antihypertensive medication into the model with all subjects included did not alter the results. Type I% predicted low blood pressure also when adjusted for cross-sectional 2003 data on physical activity, BMI, and use of alcohol in (V).
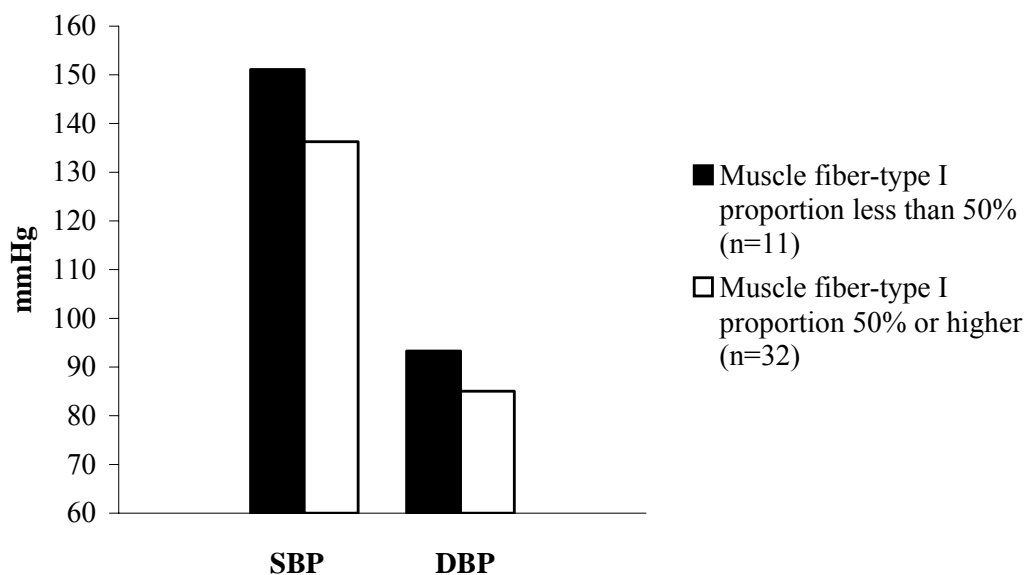
Figure 3 Mean systolic (SBP) and diastolic blood pressure (DBP) among subjects without antihypertensive medication. Significance for difference between groups: SBP, p=0.033; DBP, p=0.003 (V).

5.2.6. Effects of genetic and environmental factors on the associations between physical activity and blood pressure levels (IV, V)

Aerobic exercise during adolescence could be satisfactorily modelled by ADE, ACE, AE, and CE models. The AE model was the best fitting, and genetic effects accounted for 44% and non-shared environment for 56% of the variation in exercise (χ^2=15.30, df=13, AIC=-10.70, p=0.29). Inclusion of shared environment in the model (ACE)

reduced the proportion accounted for by genetic factors to 23%, while non-shared environment explained 59% and shared environment 18%. Lifetime aerobic exercise intensity was mostly explained by a non-shared environment, 54%, while genetics explained 46% of the variance in exercise both in the AE and the ACE models. In the AE model, the data fit well: χ^2=39.59, df=43, AIC=-46.44, p=0.62 (IV).

The bivariate model was used to assess whether the genetic and environmental effects on physical activity in adolescence correlate with genetic and environmental effects on adult blood pressure. With the correlation of the non-shared environmental effects (r_e) set at zero, the genetic correlation (r_g) was -0.40 (95% CI -0.65, -0.19, AIC -12.52). With r_g set at zero, r_e was -0.27 (95% CI -0.46, -0.12, AIC -12.40). With both correlations in the model, r_g was 0.27 (95% CI -0.57, 0.08), and r_e was -0.18 (95% CI -0.40, 0.05, AIC -12.93) (IV).

Physical activity at baseline, in 1984, was associated with diastolic blood pressure at follow-up, in 2003. When type I% was added to the model, this association disappeared (regression coefficient -0.024, p=0.66), and type I% was a significant predictor of diastolic pressure. Similar, non-significant (p=0.14, with age and BMI in 2003 in the model) results appeared for exercise in 2003 and diastolic blood pressure, and when type I% was added to the model this association also disappeared. The trends were non-significant, but in the same direction also for systolic blood pressure (V).

Type I% was a significant predictor of exercise in 2003, with a correlation of 0.47 (p<0.001) between these two characteristics. The correlation between type I% and volume of total leisure-time physical activity (including household activities) in 2003 was 0.27 (p=0.031). These results persisted also when adjusted for age. Among those whose type I% was under 50% (n=19), mean volume of exercise in 2003 was 19.4 (SEM 3.3) MET hours per week, while among those whose type I% was 50% or higher (n=45), mean volume of exercise in 2003 was 35.9 (SEM 3.5) MET hours per week; p=0.006 for difference between groups (V).

5.3. Other risk factors and hypertension or blood pressure

5.3.1. Other risk factors and hypertension or blood pressure in men (I-V)

Body mass index was consistently associated with high risk for hypertension in both the questionnaire- and register-based studies (I-III), but was not significantly associated with blood pressure in Studies IV and V. Use of alcohol was not associated with risk for hypertension in Studies I and IV, but in Studies II and III it was significantly associated with high risk (Table 10), and in Study V with high systolic blood pressure. Study IV showed no other risk factors associated with blood pressure. Having diabetes and a high BMI were, however, associated with high occurrence of hypertension, and smoking was associated with low occurrence of hypertension (IV).

Table 10 Increase in risk for hypertension (from odds ratios) for significant risk factors in men.

Study	Risk factor	Increase in risk	Adjusted for
I	BMI	12% / unit (kg/m^2) p=0.0004	Group, age
II	BMI	32% / quartile p<0.0001	Group, age, MET, alcohol, occupation
	Use of alcohol	19% /quartile p=0.018	Group, age, MET, BMI, occupation
III	Persistent overweight[a]	77%[e] p=0.001	Age, physical activity at leisure and at work, alcohol
	Increased weight[b]	57%[e] p=0.02	Age, physical activity at leisure and at work, alcohol
	Persistent heavy use of alcohol[c]	34%[f] p=0.04	Age, physical activity at leisure and at work, overweight
	Increased use of alcohol[d]	57%[f] p=0.007	Age, physical activity at leisure and at work, overweight
IV	Diabetes	734% p<0.001	Age
	BMI	12% / unit p<0.01	Age
	Smoking	-23%[g]	Age

All associations are direct, i.e., increasing risk factor elevates risk for hypertension, except for smoking in Study IV, where the association is inverse.
[a]BMI ≥ 27 in 1975 and 1981. [b]BMI <27 in 1975 and ≥ 27 in 1981. [c]Heavy use of alcohol in 1975 and 1981. [d]No heavy use of alcohol in 1975 and heavy use in 1981. [e]Compared with persistent normal weight. [f]Compared with persistently no heavy use of alcohol. [g]Compared with non-smokers.

5.3.2. Other risk factors and hypertension in women (III)

Persistent overweight and weight gain, and increased use of alcohol were significant risk factors also in women. Unlike in men, persistent heavy drinking was not a predictor of hypertension in women (Table 11) (III).

Table 11 Adjusted odds ratios (with 95% CIs) for significant risk factors in women (III).

Risk factor	Increase in risk	Adjusted for
Persistent overweight[a]	76%[d] p=0.02	Age, physical activity at leisure and at work, alcohol
Increased weight[b]	252%[d] p<0.001	Age, physical activity at leisure and at work, alcohol
Increased use of alcohol[c]	71%[e] p=0.02	Age, physical activity at leisure and at work, overweight

[a]BMI ≥ 27 in 1975 and 1981. [b]BMI <27 in 1975 and ≥ 27 in 1981. [c]No heavy use of alcohol in 1975 and heavy use in 1981. [d]Compared with persistent normal weight. [e]Compared with persistently no heavy use of alcohol.

6. DISCUSSION

6.1. Methodological issues

6.1.1. General

Randomized controlled trials (RCT) are considered the gold standard in studies on therapy or prevention of any condition (Guyatt et al. 1993). This design is, however, not always applicable. It is, for example, unthinkable to perform an RCT instead of an observational study when the effects of life-long engagement in leisure-time physical activity or those of very vigorous, competitive, exercise training are assessed. Some selection processes may, in fact, be present in RCTs as well. If, for example, effects of a physical activity intervention are to be studied, it is possible that those who dislike exercise won't agree to participate.

When interpreting results from observational studies and from non-randomized intervention studies, it should be recognized that because of selection issues, non-randomized studies tend to show larger treatment and prevention effects than do randomized trials (Guyatt et al. 1993). Regarding the present studies, elite athletes, and to a lesser extent also those who engage in recreational leisure-time physical activity, are a socially, psychologically, biologically, and genetically select group, and the same selection may explain low morbidity in these groups (Kujala et al. 2003).

6.1.2. Validity and reliability of physical activity and hypertension variables

For the classifications of hypertension in Studies I to III, comparisons of questionnaire responses and blood pressure measurements, though being only indirect measures, supported the validity of the data. These results are in agreement with findings of Haapanen et al. (1997a) that questionnaire-provided data and medical records from health centres and one central hospital in Finland are in good agreement.

No validation studies exist for the data on physical activity in Studies I to III. In studies on the same cohort as in Study III, where physical activity data were based on the same questions, physical activity was, however, a significant predictor of mortality (Kujala et al. 1998, Kujala et al. 2002).

For the interview data on physical activity in Study IV, the repeatability of the interviewed replies on sport and exercise habits during a 5-year test-retest interval appears in Ropponen et al. (2001). For exercise years and mean hours per week by mode for the most commonly performed exercise type during one defined time period, the mean intraclass correlation coefficients (ICC) ranged from 0.63 to 0.90, and for the sum of all lifetime exercises reported, mean ICCs were 0.69 to 0.73. For exercise intensity, the repeatability was lower (mean kappa 0.33 to 0.48). The validity of the data has not, however, been assessed.

The reliability of the Kuopio Ischemic Heart Disease Study 12-month physical activity questionnaire in Study V has been assessed (Lakka and Salonen 1992, Lakka and Salonen 1993). For repeatability of the data on total energy expenditure and both total physical activity and only conditioning activities, the ICCs were 0.57 to 0.58 The

regression coefficient between energy expenditure in jogging and skiing, and maximal oxygen uptake was 0.28 ($p<0.05$) (Salonen and Lakka 1987), and the correlation between total energy expenditure and maximal oxygen uptake was 0.23 (Lakka and Salonen 1993).

6.2. Physical activity and blood pressure or risk for hypertension

6.2.1. Physical activity and risk for hypertension

Engagement in vigorous activity earlier in life is associated in men with low risk for hypertension. The risk for hypertension was in master orienteers one-quarter that of controls (age-adjusted OR 0.26), and this difference remained significant also after adjusting for age, alcohol-use, smoking, and body mass index (I). Having been an elite athlete in endurance or mixed sports was also associated with low incidence of hypertension. What should be kept in mind is the considerable difference in the prevalence of hypertension between the endurance and mixed sports group and the controls in 1985 (21.9% vs. 28.6%) (Kujala et al. 1994), and the fact that persons with a history of hypertension in 1985 were excluded from the present study. Thus, the differences in incidence of hypertension between 1986 and 1995 may have been diluted. Despite this, the result was significant, which strengthens the evidence that having been an endurance or mixed sports top athlete predicts low incidence of hypertension (II). In the twin cohort, vigorous physical activity was, in men, independently associated with low risk for hypertension. Adjusted for all covariates (age, alcohol-use, smoking, and overweight), persistent non-participation in vigorous activity was associated with an increase in risk for hypertension of 60% during the 9-year period starting in 1982 compared to persistent participation. Interestingly, non-participation only in 1975 or in 1981 was not associated with increased risk (III).

The results on volume of physical activity and risk for hypertension were inconsistent. For the former elite athletes and controls, high volume of activity was associated with low risk (II), but the twins showed no such association (III). In the study with the subgroup of twins, where data were collected cross-sectionally, only engagement in other sports (other than aerobic- or power-type sports) was associated with low prevalence of hypertension. No other physical activity variables were associated with prevalence of hypertension (IV).

The literature agrees on physical activity's being associated with low risk for hypertension in men, but there exists some controversy concerning intensity of physical activity and risk for hypertension. Several reports, including prospective studies in which the endpoint was questionnaire-based (Paffenbarger et al. 1983, 1991) and a cross-sectional study with blood pressure measured (MacAuley et al. 1996), show that in men, both vigorous activity and physical activity volume are associated with low risk for hypertension or low blood pressure. Pereira and co-workers (1999) have found, in a prospective study in which blood pressure was measured and use of medication for hypertension determined by questionnaire, that in white males, the volume of activity is important but vigorous activity is not. Haapanen et al. (1997b) reported, in a prospective questionnaire- and register-based study, that both intensity and volume of physical activity were separately associated with low risk for hypertension, but when they were both in the model, intensity was

no longer important. In contrast, in the present study on twins, participation in vigorous activity was strongly associated with low risk for hypertension in men whereas volume of activity was unimportant.

One difference between the present study and some studies that have found an association between volume of physical activity and hypertension is the level of the cut-off point. In the present study, those subjects whose volume of activity corresponded to ≥30 minutes of walking per day were classified as physically active during their leisure time (III). In those studies (Paffenbarger et al. 1983, Haapanen et al. 1997b) from which the volume of activity used as cut-off point can be assessed from the data in the report, the cut-off point was set at about twice as large a volume of activity as in the present study. However, when the cut-off point in the present study was changed from 2 MET hours per day to 4 MET hours per day, and the data were re-analysed post hoc, still no association appeared between volume of physical activity and hypertension (results not shown). Such inconsistencies in the findings may be due to difficulties in measurement of physical activity (LaPorte et al. 1985, Powell et al. 1987, Kriska and Caspersen 1997, Lamonte and Ainsworth 2001).

Women showed no associations between intensity or volume of physical activity and risk for hypertension (III), consistent with some earlier findings (Haapanen et al. 1997b, Pereira et al. 1999); other studies have found an association between women's physical activity and blood pressure (Folsom et al. 1990, Reaven et al. 1991, MacAuley et al. 1996, Levenstein et al. 2001).

One explanation for the present findings differing between men and women may be that the effect of physical activity in women and in men is not similar. Another possible explanation may be the differing physical activity habits between men and women. The numbers having different patterns of physical activity volume are rather similar for men and women, but for vigorous activity, the numbers differ markedly. Whereas 25% of the men were persistently participating in vigorous activity, the corresponding percentage for women was as low as 6%. Moreover, of those exercising vigorously, a much larger percentage of men were engaged in activity with an intensity corresponding to running instead of jogging compared with women: 42.7% vs. 16.9% in 1975, and 39.1% vs. 22.3% in 1981 (III). In both studies (Haapanen et al. 1997b, Pereira et al. 1999) that found no association between physical activity and hypertension, the activity patterns of women and men differed similarly to the patterns in the present study. In the Finnish cohort studied by Haapanen and co-workers (1997b), the intensity of physical activity in women was much lower than in men and total volume somewhat lower. In Pereira et al. (1999), a similar proportion of white men and women reported exercising, but the proportion of men reporting sweating during their leisure time was more than twice as large as among women, which may indicate that men engaged in vigorous activity more often than women. Because intervention studies show that exercise training-induced reductions in blood pressure are larger and more consistent in women than in men (Hagberg et al. 2000), it seems plausible to assume that physical activity might be effective in preventing hypertension in women if their exercise patterns were similar to men's, as to be seen with mortality (Blair et al. 1993, Blair 1996). Most questionnaires used in epidemiologic studies have been developed for men and may, because of differing types of activities between the sexes, lead to misclassification of

physical activity in women (Blair 1996). It has been reported (Blair et al. 1993) that whereas treadmill-measured fitness predicts death equally well in men and in women, self-reported activity in the same cohort predicts mortality only in men, suggesting that the measurement of physical activity in women is inadequate (Blair et al. 1993).

6.2.2. Physical activity and blood pressure levels

In the male twins, aerobic exercise in adolescence and lifetime high-intensity aerobic exercise were associated with low diastolic blood pressure in adulthood. No leisure-time physical activity variables were associated with low systolic blood pressure; regular participation in aerobic exercise during the past year was, however, surprisingly, associated with high levels of systolic blood pressure (IV). In the study on muscle fibre type, physical activity in 1984 was associated with low diastolic blood pressure at follow-up, in 2003 (V).

The finding that specifically aerobic exercise in adolescence is associated with low diastolic blood pressure in adulthood is new. Four European cohort studies (Twisk et al. 2002b, Boreham et al. 2002, Hasselstrøm et al. 2002, Lefevre et al. 2002) following subjects from youth to adulthood have explored the associations between physical activity in adolescence and blood pressure in adulthood. Physical activity levels were assessed at 12 to 19 years of age, and the blood pressure of the same subjects was later measured at the age of 20 to 40, but revealed no associations between physical activity in youth and low blood pressure in adulthood. One study (Barnekow-Bergkvist et al. 2001) has found a relationship between a positive attitude toward aerobic exercise in adolescence and decreased risk for high systolic blood pressure (diastolic blood pressure not reported). In that study, leisure-time sports activity in adolescence was not associated with low risk for elevated systolic blood pressure, which was, however, a dichotomized classification.

In the studies finding no associations between physical activity in youth and blood pressure in adulthood, activity included all kinds of physical activity, aerobic exercise as well as speed- and strength-demanding activities; the present study examined aerobic exercise separately. Furthermore, the subjects were younger at follow-up than were those in the present study (age 20 to 40 vs. 35 to 70) (Barnekow-Bergkvist et al. 2001, Twisk et al. 2002b, Boreham et al. 2002, Hasselstrøm et al. 2002, Lefevre et al. 2002). Another factor that may contribute to the findings of no association can be inaccuracy in measuring physical activity, especially its intensity, which is often used in calculation of total physical activity (Twisk et al. 2002a, Ropponen et al. 2001).

The findings that regular aerobic exercise during the past year was associated with elevated systolic blood pressure and that otherwise no associations appeared between present engagement in aerobic exercise and blood pressure are contradictory to earlier findings. An association between physical activity and low risk for hypertension has been found (Paffenbarger et al. 1983, Paffenbarger et al. 1991, Haapanen et al. 1997b, Pereira et al.1999), as well as between physical activity and low blood pressure (MacAuley et al. 1996, Wareham et al. 2000). No clear explanations exist for the present findings. One possibility is that those who have had elevated blood pressure readings may have been advised by their physicians to exercise. These results may also reflect the difficulties in assessing lifetime physical activity; perhaps the

classification of physical activity in adolescence was more accurate than that of adulthood physical activity.

6.3. Effects of genetic and environmental factors on physical activity, blood pressure levels, and their associations

Interindividual genetic differences accounted for 35% and aerobic exercise in adolescence alone explained 5% of the variance in diastolic blood pressure in adulthood. In turn, genetic factors explained 44% and the environment 56% of the total variance of aerobic exercise in adolescence. High intensity aerobic exercise during the whole lifetime was also associated with low diastolic blood pressure in adulthood. However, when the effect of this variable on diastolic pressure was assessed together with genetic and environmental effects, it was not significant. No physical activity variables were associated with systolic blood pressure, 39% of which was explained by genetic effects (IV).

Several studies have demonstrated that blood pressure is in part genetically determined (Fagard et al. 1995, Luft 2001). The present results are concordant with the earlier estimates of the proportion of variation in blood pressure explained by genetics as ranging from 15 to 73% (Hunt el al. 1989, Koskenvuo et al. 1992, Hong et al 1994, Schork et al. 1994, Fagard et al. 1995, Snieder et al. 2000, Livshits et al. 2001, Vinck et al. 2001, Iliadou et al. 2002, Evans et al. 2003). Furthermore, intervention studies show large variations between individuals in resting blood pressure response to exercise training. Genetic effects account for part of these variations; consistently for systolic and somewhat inconsistently for diastolic blood pressure (Hagberg et al. 1999, An et al. 2000, Rauramaa et al. 2002, Rice et al. 2002, Zhang et al. 2002, Kimura et al. 2003).

The same genetic factors associated with participation in aerobic exercise in adolescence seemed to be associated with low diastolic blood pressure in adulthood. Three different bivariate models fit the data about equally well. The ability to distinguish between well-fitting models depends on the number of subjects in the study. Since this number is not very large in the present study, it cannot be concluded which one of the three models is the best, and thus the general conclusion is that both genetic effects and non-shared environmental effects accounting for aerobic exercise in adolescence on the one hand, and diastolic blood pressure on the other seem to be correlated (IV).

Muscle fibre proportion may in part explain the correlation between the genetic effects of physical activity and those of blood pressure. Fibre proportion determined at baseline in 1984 was a significant predictor of blood pressure at follow-up in 2003. A high proportion of type I fibres (type I%) was associated with low systolic and low diastolic blood pressures. This association persisted also after adjusting for other baseline data, i.e., physical activity and BMI in 1984. The association between type I% and blood pressure was unchanged also when adjusting for exercise, BMI, and use of alcohol in 2003 (V). The fact that type I% predicts volume of exercise, and that the trend between exercise in 2003 and diastolic blood pressure was lost when including muscle type distribution into the model, indicates that the known association between exercise and low blood pressure or exercise and low risk for hypertension (Blair et al.

1984, Paffenbarger et al. 1983, 1991) may at least in part be due to fibre-type distribution, with exercise acting as a confounding factor in this association (V).

Type I% is mostly determined by genetic factors (Komi et al. 1977, Simoneau and Bouchard 1995) and is rather resistant to change with alterations in aerobic activity (Bassett 1994, Simoneau and Bouchard 1995, Spangenburg and Booth 2003) and with ageing (Rogers and Evans 1993). Hence, muscle fibre distribution may cause a genetic selection bias in observational studies on exercise and hypertension, and also on exercise and coronary heart disease or stroke (Kujala et al. 2003), since hypertension is an important risk factor for these diseases (Collins et al. 1990, MacMahon et al. 1990, Franklin et al. 1999, Domanski et al. 2001).

Furthermore, the result that, in men, participation in vigorous activity only in 1975 was not associated with increased risk for hypertension between 1982 and 1990 (adjusted OR 0.96) compared with persistent participation (both in 1975 and in 1981) (III) may imply that the genetic component is also important in the association between vigorous physical activity and low risk for hypertension. It could be thought that, due to inherited characteristics, those who are physically active and are engaged in vigorous activity would be at low risk for hypertension even if they were not physically active. One test of this hypothesis would be to examine twin pairs discordant for physical activity, as they share all (for MZ pairs) or some (for DZ pairs) of their genes. Using this design, Kujala et al. (2000) have shown that physical activity is associated with reduced risk for type 2 diabetes, and with reduced risk for overall mortality in DZ, but not in MZ pairs (Kujala et al. 2002). The current sample, however, comprised too few pairs discordant for both physical activity and incident hypertension for meaningful analyses.

## 6.4. Other risk factors and hypertension or blood pressure

High BMI was consistently associated with high risk for hypertension both in men and in women (I-IV). In Studies IV and V, BMI was, however, not associated with measured blood pressure. High BMI is known to be a risk factor for hypertension (Stamler et al. 1978, Havlik et al. 1983, Paffenbarger et al. 1983). Heavy alcohol-use and diabetes were also associated with increased risk for hypertension and increased blood pressure (II-V), in accordance with the literature (MacMahon 1987, Stamler et al 1997, Sowers et al. 2001, Stamler et al. 2002).

7. CONCLUSIONS AND FUTURE PROSPECTS

The key findings of the present study are as follows:

1. Long-term vigorous, competitive endurance activity in adulthood is associated with a markedly lower occurrence of hypertension compared with that of a control population. This association is independent of body mass index. Natural propensities and the process of becoming an elite athlete in endurance or mixed sports are associated with low risk for hypertension in middle age. Both selection to these sports and continuity of endurance training may play a role in explaining this low risk for hypertension.

2. In an unselected population, long-term engagement in vigorous physical activity is independently associated with reduced risk for hypertension in men compared with persistent non-engagement. Changes in engagement in vigorous physical activity were not associated with increased risk for hypertension compared with persistent engagement. Women showed no association between physical activity and risk for hypertension, which may be in part due to differing patterns of exercise with gender.

3. The heritable components of aerobic physical activity in adolescence and of diastolic blood pressure levels in adulthood are correlated.

4. A high proportion of type I (slow-twitch) muscle fibres in skeletal muscle is a strong predictor of low blood pressure levels. The association between type I% and blood pressure is independent of physical activity levels and body mass index. Type I% also predicts physical activity levels, and partially explains the association between physical activity and low blood pressure levels.

Consideration as to whether genetic selection explains some of the associations between physical activity and health seen in observational studies is increasing (Kujala et al. 2003). The present study offers some answers regarding hypertension. In men, most information obtainable by observational twin studies has already been processed. Now, short-term and long-term intervention studies concerning the effect of exercise training and genetic factors on blood pressure levels and risk for hypertension should be conducted. And finally, the specific genes in part accounting for the association between high physical activity and low blood pressure levels should be identified.
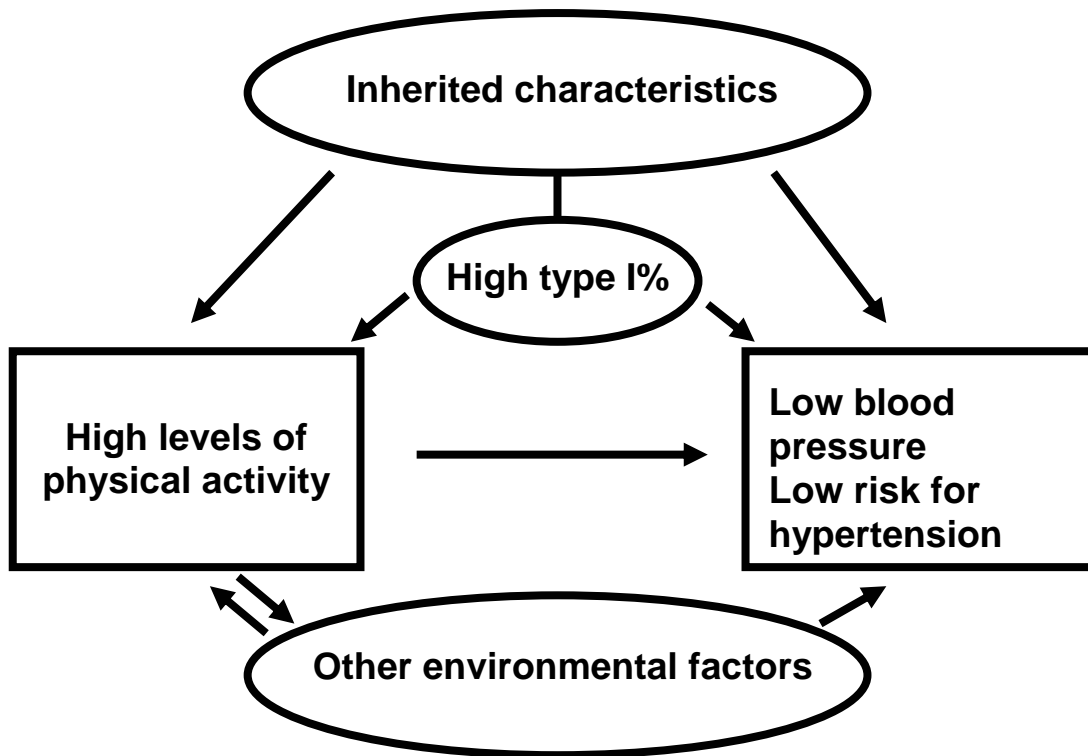
Figure 4 Associations between physical activity, other environmental factors, inherited characteristics, and blood pressure and hypertension. Type I%=proportion of type I muscle fibres.

ACKNOWLEDGEMENTS

This work was carried out at the Unit for Sports and Exercise Medicine, Institute of Clinical Medicine, and at the Department of Public Health, both at the University of Helsinki, Finland.

I am extremely grateful to my excellent supervisors, Professors Urho Kujala and Jaakko Kaprio. They have been the best supervisors one could imagine. It is a privilege to have had the opportunity to be taught and guided by them. They both always had time for me, answered my questions and corrected my mistakes patiently again and again, and very skilfully gave me more responsibility for the studies little by little as the project advanced. Their knowledge of their scientific fields is extremely impressive.

Professor Seppo Sarna deserves my sincere thanks for his valuable help with statistics. Docent Jouko Karjalainen helped much in the preparation of the manuscripts. Professors Tapio Videman and Michele Battié receive thanks for their valuable advice and opinions.

All these are warmly thanked for allowing me to use the data on master orienteers, former elite athletes, the twin cohort, and the subgroup of the twin cohort.

I want to express my deepest gratitude to Docent Heikki Tikkanen for all his help. He initiated and pursued the muscle fibre-type distribution study, and was also a key person in the second part of that study. He supported me and gave me valuable advice on science, sports, and medicine when I most needed it.

Professor Timo Lakka and Docent Timo Kuusi are truly appreciated for their thorough and most helpful review of this thesis. Their comments and suggestions improved the thesis significantly.

Esko Levälahti, Riitta Simonen, and Arja Uusitalo-Koskinen also deserve my sincere thanks for their work and expertise.

I warmly thank Juha Peltonen for his generous help with large and small scientific and technical problems. He knows everything there is to know about exercise physiology. We also had many inspiring and relaxing talks about sports and life itself.

I want to thank Maija Kopo for skilful measurements and also for all the help with practical matters, with which Minna Riitamaa and Ulla Nypelö also helped me a lot.

My sincere thanks to Carol Norris for skilful author's-editing of this thesis while ill.

I am extremely thankful to all my friends who have more or less directly helped me with this work, with science, with presentations, and most importantly, with life and everything there is to it. Thank you all; you know who you are.

And last but not least, I am always grateful to my family for their never-ending support in every imaginable way. Without them, this would never have been possible!

Helsinki, September 2004

Miika Hernelahti

REFERENCES

Aaron DJ, LaPorte RE. Physical activity, adolescence, and health: an epidemiological perspective. Exerc Sport Sci Rev 1997; 25: 391-405.

Abe H, Kawano Y, Kojima S, Ashida T, Kuramochi M, Matsuoka H, Omae T. Biphasic effects of repeated alcohol intake on 24-hour blood pressure in hypertensive patients. Circulation 1994; 89: 2626-2633.

Abramson JL, Weintraub WS, Vaccarino V. Association between pulse pressure and c-reactive protein among apparently healthy US adults. Hypertension 2002; 39: 197-202.

Agabiti Rosei EA, Rizzoni D, Castellano M, Porteri E, Zulli R, Muiesan ML, Bettoni G, Salvetti M, Muiesan P, Giulini SM. Media : lumen ratio in human small resistance arteries is related to forearm minimal vascular resistance. J Hypertens 1995; 13: 341-347.

Ainslie PN, Reilly T, Westerterp KR. Estimating human energy expenditure. A review of techniques with particular reference to doubly labelled water. Sports Med 2003; 33: 683-698.

Ainsworth BE, Keenan NL, Strogatz DS, Garrett JM, James SA. Physical activity and hypertension in black adults: the Pitt County Study. Am J Public Health 1991; 81: 1477-1479.

Allender PS, Cutler JA, Follmann D, Cappuccio FP, Pryer J, Elliott P. Dietary calcium and blood pressure: a meta-analysis of randomized clinical trials. Ann Intern Med 1996; 124: 825-831.

Amigoni S, Morelli P, Parazzini F, Chatenoud L. Determinants of elevated blood pressure in women around menopause: results from a cross-sectional study in Italy. Maturitas 2000; 34: 25-32.

An P, Rice T, Gagnon J, Borecki IB, Pérusse L, Leon AS, Skinner JS, Wilmore JH, Bouchard C, Rao DC. Familial aggregation of resting blood pressure and heart rate in a sedentary population: the HERITAGE Family Study. Am J Hypertens 1999; 12: 264-270.

An P, Rice T, Pérusse L, Borecki IB, Gagnon J, Leon AS, Skinner JS, Wilmore JH, Bouchard C, Rao DC. Complex segregation analysis of blood pressure and heart rate measured before and after a 20-week endurance exercise training program: the HERITAGE Family Study. Am J Hypertens 2000; 13: 488-497.

Andersen JL, Schjerling P, Saltin B. Muscle, genes and athletic performance. Sci American 2000; 283: 48-55.

Andersen P. Capillary density in skeletal muscle of man. Acta Physiol Scand 1975; 95: 203-205.

Andrews G, MacMahon SW, Austin A, Byrne DG. Hypertension: comparison of drug and non-drug treatments. BMJ 1982; 284: 1523-1526.

Arkwright PD, Beilin LJ, Rouse I, Armstrong BK, Vandongen R. Effects of alcohol use and other aspects of lifestyle on blood pressure levels and prevalence of hypertension in a working population. Circulation 1982; 66: 60-66.

Aromaa A. Kohonnut verenpaine ja sen kansanterveydellinen merkitys Suomessa. Academic Dissertation. Kansaneläkelaitoksen julkaisuja AL: 17, Helsinki, Finland 1981.

Ashley FW, Kannel WB. Relation of weight change to changes in atherogenic traits: the Framingham Study. J Chron Dis 1974: 27: 103-114.

Barlassina C, Lanzani C, Manunta P, Bianchi G. Genetics of essential hypertension: from families to genes. J Am Soc Nephrol 2002: 13: S155-S164.

Barlassina C, Schork NJ, Manunta P, Citterio L, Sciarrone MT, Lanella G, Bianchi G, Cusi D. Synergistic effect of alpha-adducin and ACE genes in causing blood pressure changes with body sodium and volume expansion. Kidney Int 2000; 57 (Suppl 3): 1083-1090.

Barnard RJ, Edgerton VR, Furukawa T, Peter JB. Histochemical, biochemical and contractile properties of red, white and intermediate fibers. Am J Physiol 1971; 220: 410-414.

Barnekow-Bergkvist M, Hedberg G, Janlert U, Jansson E. Adolescent determinants of cardiovascular risk factors in adult men and women. Scand J Publ Health 2001; 29: 208-217.

Bassett DR Jr, Fitzhugh EC, Crespo CJ, King GA, McLaughlin JE. Physical activity and ethnic differences in hypertension prevalence in the United States. Prev Med 2002; 34: 179-186.

Bassett Jr DR. Skeletal muscle characteristics: relationships to cardiovascular risk factors. Med Sci Sports Exerc 1994; 26: 957-966.

Battié MC, Haynor D, Gill K, Fisher L, Gibbons L, Videman T. Similarities in degenerative findings on MRIs of the lumbar spine of identical twins. J Bone Joint Surg (Am) 1995; 77: 1662-1670.

Battié MC, Videman T, Gibbons LE, Fisher LD, Manninen H, Gill K. Determinants of lumbar disc degeneration: A study relating lifetime exposures and MRI findings in identical twins. Spine 1995: 21; 2601-2612.

Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetière P, Guize L. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. Hypertension 1997; 30: 1410-1415.

Bergh U, Thorstensson A, Sjödin B, Hulten B, Piehl K, Karlsson J. Maximal oxygen uptake and muscle fibre types in trained and untrained humans. Med Sci Sports 1978; 10:151-154.

Berglund G, Wilhelmsen L, Werkö L. Blood pressure development and characteristics of subjects with moderate blood pressure elevation. Acta Med Scand 1974; 196: 301-306.

Berglund G, Wilhelmsen L. Factors related to blood pressure in a general population sample of Swedish men. Acta Med Scand 1975; 198: 291-298.

Beunen G, Thomis M. Genetic determinants of sports participation and daily physical activity. Int J Obes 1999; 23 (Suppl 3): S55-S63.

Bijnen FCH, Feskens EJM, Caspersen CJ, Giampaoli S, Nissinen AM, Menotti A, Mosterd WL, Kromhout D. Physical activity and cardiovascular risk factors among elderly men in Finland, Italy, and The Netherlands. Am J Epidemiol 1996; 143: 553-561.

Biron P, Mongeau JG, Bertrand D. Familial aggregation of blood pressure in 558 adopted children. Can Med Assoc J 1976; 115: 773-774.

Blair SN, Brodney S. Effects of physical inactivity and obesity on morbidity and mortality: current evidence and research issues. Med Sci Sports Exerc 1999; 31 (suppl): S646-S662.

Blair SN, Goodyear NN, Gibbons LW, Cooper KH. Physical fitness and incidence of hypertension in healthy normotensive men and women. JAMA 1984; 252: 487-490.

Blair SN, Kampert JB, Kohl HW, Barlow CE, Macera CA, Paffenbarger RS Jr, Gibbons LW. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA 1996; 276: 205-210.

Blair SN, Kohl HW, Barlow CE. Physical activity, physical fitness, and all-cause mortality in women: do women need to be active? J Am Coll Nutr 1993; 12: 368-371.

Blaustein MP, Hamlyn JM. Pathogenesis of essential hypertension: a link between dietary salt and high blood pressure. Hypertension 1991; 18: Suppl 3: 184-195.

Bonnardeaux A, Davies E, Jeunemaitre X, Fery I, Charru A, Clauser E, Tiret L, Cambien F, Corvol P, Soubrier F. Angiotensin II type 1 receptor gene polymorphisms in human essential hypertension. Hypertension 1994; 24: 63-69.

Boomsma DI, van den Bree MBM, Orlebeke JF, Molenaar PCM. Resemblances of parents and twins in sports participation and heart rate. Behav Gen 1989; 19: 124-141.

Boreham C, Twisk J, Neville C, Savage M, Murray L, Gallagher A. Associations between physical fitness and activity patterns during adolescence and cardiovascular risk factors in young adulthood: the Northern Ireland Young Hearts Project. Int J Sports Med 2002; 23 (Suppl): S22-S26.

Bos WJW, van der Meiracker AH, Wesseling KH, Schalekamp MADH, Effect of regional and systemic changes in vasomotor tone on finger pressure amplification. Hypertension 1995; 26: 315-320.

Bouchard C, Rankinen T. Individual differences in response to regular physical activity. Med Sci Sports Exerc 2001; 33 (Suppl.): S446-S451.

Bouchard C, Shephard RJ. Physical activity, fitness and health: the model and key concepts. In: Bouchard C, Shephard RJ, Stephens T (editors): Physical activity, fitness and health. International proceedings and consensus statement. Champaign Illinois: Human Kinetics Publishers: 1994: 77-88.

Bouchard C, Simoneau J-A, Lortie G, Boulay MR, Marcotte M, Thibault M-C. Genetic effects in human skeletal muscle fiber type distribution and enzyme activities. Can J Physiol Pharmacol 1986; 64: 1245-1251.

Brooke MH, Kaiser KK. Muscle fiber types: How many and what kind? Arch Neurol 1970; 23: 369-379.

Burke RE, Levine DN, Zajac FE, Tsairis P, Engel WK. Mammalian motor units: physiological-histochemical correlation in three types in cat gastrocnemius. Science 1971; 174: 709-712.

Burke V, Beilin LJ, Grosskopf GS, Ritchie J, Puddey IB, Rogers P. Association of lifestyle and personality characteristics with blood pressure and hypertension: a cross-sectional study in the elderly. J Clin Epidemiol 1992; 45: 1061-1070.

Byberg L, Zethelius B, McKeigue PM, Lithell HO. Changes in physical activity are associated with changes in metabolic cardiovascular risk factors. Diabetologia 2001; 44: 2134-2139.

Cameron JD, Dart AM. Exercise training increases total systemic arterial compliance in humans. Am J Physiol 1994; 266 (Heart Circ Physiol): H693-H701.

Carroll S, Cooke CB, Butterly RJ. Metabolic clustering, physical activity and fitness in nonsmoking, middle-aged men. Med Sci Sports Exerc 2000; 32: 2079-2086.

Castellano M, Rossi F, Giacchè M, Perani C, Rivadossi F, Muiesan ML, Salvetti M, Beschi M, Rizzoni D, Agabiti-Rosei E. β_2-adrenergic receptor gene polymorphism, age, and cardiovascular phenotypes. Hypertension 2003; 41: 361-367.

Cederholm J, Wibell L. The relationship of blood pressure to blood glucose and physical leisure time activity. A study of hypertension in a survey of middle-aged subjects in Uppsala 1981-1982. Acta Med Scand 1986; 219: 37-46.

Christian JC, Williams CJ. Comparison of analysis of variance and likelihood models of twin data analysis. In: Spector TD, Snieder H, MacGregor AJ, eds. Advances in twin and sib-pair analysis. Oxford, United Kingdom: Oxford University Press 2000: 103-118.

Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. Br Med Bull 1994;50: 272-298.

Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH. Blood pressure, stroke, and coronary heart disease, part 2: effects of short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990; 335: 827-838.

Convertino VA. Blood volume: its adaptation to endurance training. Med Sci Sports Exerc 1991; 23: 1338-1348.

Cooper KH, Pollock ML, Martin RP, White SR, Linnerud AC, Jackson A. Physical fitness levels vs selected coronary risk factors. A cross-sectional study. JAMA 1976; 236: 166-169.

Costill DL, Daniels J, Evans W, Fink W, Krahenbuhl G, Saltin B. Skeletal muscle enzymes and fibre composition in male and female track athletes. J Appl Physiol 1976; 90: 149-154.

Costill DL, Fink WJ, Pollock ML. Muscle fiber composition and enzyme activities of elite distance runners. Med Sci Sports 1976; 8: 96-100.

Cowley AW Jr, Roman RJ. The role of the kidney in hypertension. JAMA 1996; 275: 1581-1589.

Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: an overview. Am J Clin Nutr 1997; 65 (Suppl): 643S-651S.

Davidson K, Jonas BS, Dixon KE, Markovitz JH. Do depression symptoms predict early hypertension incidence in young adults in the CARDIA Study? Arch Intern Med 2000; 160: 1495-1500.

Devereux RB, Pickering TG, Alderman MH, Chien S, Borer JS, Laragh JH. Left ventricular hypertrophy in hypertension. Prevalence and relationship to pathophysiologic variables. Hypertension 1987; 9: II-53-II-60.

Devereux RB. Cardiac involvement in essential hypertension. Prevalence, pathophysiology and prognostic implications. Med Clin N Am 1987; 71: 813-825.

Doan AE, Peterson DR, Blackmon JR, Bruce RA. Myocardial ischemia after maximal exercise in healthy men. One year follow-up of physically active and inactive men. Am J Cardiol 1966; 17: 9-19.

Domanski M, Norman J, Wolz M, Mitchell G, Pfeffer M. Cardiovascular risk assessment using pulse pressure in the First National Health and Nutrition Examination Survey (NHANES I). Hypertension 2001; 38: 793-797.

Dyer AR, Stamler J, Paul O, Berkson DM, Lepper H, McKean RB, Shekelle RB, Lindberg HA, Garside D. Alcohol consumption, cardiovascular risk factors and mortality in two Chicago epidemiologic studies. Circulation 1977; 56: 1067-1074.

Dyer AR, Stamler J, Shekelle RB, Schoenberger J. The relationship of education to blood pressure: findings on 40,000 employed Chicagoans. Circulation 1976; 54: 987-992.

Elliot P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, Marmot M. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. BMJ 1996; 312: 1249-1253.

Esler M. The sympathetic system and hypertension. Am J Hypertens 2000; 13: 99S-105S.

Essen B, Jansson E, Henriksson J, Taylor AW, Saltin B. Metabolic characteristics of fibre types in human skeletal muscle. Acta Physiol Scand 1975; 95: 153-165.

Evans A, van Baal GCM, McCarron P, deLange M, Soerensen TIA, de Geus EJC, Kyvik K, Pedersen NL, Spector TD, Andrew T, Patterson C, Whitfield JB, Zhu G, Martin NG, Kaprio J, Boomsma DI. The genetics of coronary heart disease: the contribution of twin studies. Twin Res 2003; 6: 432-441.

Fagard R, Brguljan J, Staessen J, Thijs L, Derom C, Thomis M, Vlietinck R. Heritability of conventional and ambulatory blood pressures. A study in twins. Hypertension 1995; 26: 919-924.

Fagard RH, Tipton CM. Physical activity, fitness and hypertension. In: Bouchard C, Shephard RJ, Stephens T (editors): Physical activity, fitness and health. International proceedings and consensus statement. Champaign Illinois: Human Kinetics Publishers: 1994: 633-655.

Fagard RH. Exercise characteristics and the blood pressure response to dynamic physical training. Med Sci Sports Exerc 2001; 33 (Suppl): S484-S492.

Fagard RH. Physical activity in the prevention and treatment of hypertension in the obese. Med Sci Sports Exerc 1999; 31 (Suppl): S624-S630.

Fagard RH. Prescription and results of physical activity. J Cardiovasc Pharmacol 1995; 25 (Suppl 1): S20-S27.

Fang J, Wylie-Rosett J, Cohen HW, Kaplan RC, Alderman MH. Exercise, body mass index, caloric intake, and cardiovascular mortality. Am J Prev Med 2003; 25: 283-289.

Fardy PS, Maresh CM, Abbott RD. A comparison of myocardial function in former athletes and non-athletes. Med Sci Sports 1976; 8: 26-30.

Felmeden DC, Spencer CGC, Blann AD, Beevers DG, Lip GYH. Physical activity in relation to indices of endothelial function and angiogenesis factors in hypertension: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). J Intern Med 2003; 253: 81-91.

Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, Pedrinelli R, Brandi L, Bevilacqua S. Insulin resistance in essential hypertension. N Engl J Med 1987; 317: 350-357.

Ferrannini E, Natali A, Capaldo B, Lehtovirta M, Jacob S, Yki-Järvinen H. Insulin resistance, hyperinsulinemia, and blood pressure: role of age and obesity. Hypertension 1997; 30: 1144-1149.

Folkow B. Hypertensive structural changes in systemic precapillary resistance vessels: how important are they for in vivo haemodynamics? J Hypertens 1995; 13: 1546-1559.

Folsom AR, Caspersen CJ, Taylor HL, Jacobs DR Jr, Luepker RV, Gomez-Marin O, Gillum RF, Blackburn H. Leisure time physical activity and its relationship to coronary risk factors in a population-based sample. The Minnesota Heart Survey. Am J Epidemiol 1985; 121: 570-579.

Folsom AR, Prineas RJ, Kaye SA, Munger RG. Incidence of hypertension and stroke in relation to body fat distribution and other risk factors in older women. Stroke 1990; 21: 701-706.

Fornage M, Amos CI, Kardia S, Sing CF, Turner ST, Boerwinkle E. Variation in the region of the angiotensin-converting enzyme gene influences interindividual differences in blood pressure levels in young white males. Circulation 1998; 97: 1773-1779.

Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. Circulation 1999; 100: 354-360.

Franks PW, Bhattacharyya S, Luan J, Montague C, Brennand J, Challis B, Brage S, Ekelund U, Middelberg RPS, O'Rahilly S, Wareham NJ. Association between physical activity and blood pressure is modified by variants in the G-protein coupled receptor 10. Hypertension 2004; 43: 224-228.

Frisk-Holmberg M, Essén B, Fredrikson M, Ström G, Wibell L. Muscle fibre composition in relation to blood pressure response to isometric exercise in normotensive and hypertensive subjects. Acta Med Scand 1983; 213:21-26.

Frisk-Holmberg M, Jorfeldt L, Juhlin-Dannfelt A, Karlsson J. Leg blood flow during exercise in man in relation to muscle fibre composition. Acta Physiol Scand 1981; 112: 339-342.

Frost CD, Law MR, Wald NJ. By how much does dietary salt reduction lower blood pressure? II - Analysis of observational data within populations. BMJ 1991; 302: 815-818.

Fuentes RM, Perola M, Nissinen A, Tuomilehto J. ACE gene and physical activity, blood pressure, and hypertension: a population study in Finland. J Appl Physiol 2002; 92: 2508-2512.

de Gaudemaris R, Lang T, Chatellier G, Larabi L, Lauwers-Cancés V, Maitre A, Diène E. Socioeconomic inequalities in hypertension prevalence and care: the IHPAF study. Hypertension 2002; 39: 1119-1125.

Giannattasio C, Cattaneo BM, Mangoni AA, Carugo S, Sampieri L, Cuspidi C, Grassi G, Mancia G. Changes in arterial compliance induced by physical training in hammer-throwers. J Hypertens 1992; 10 (suppl 6): S53-S56.

Gibbons LW, Blair SN, Cooper KH, Smith M. Association between coronary heart disease risk factors and physical fitness in healthy adult women. Circulation 1983; 67: 977-983.

Guidelines Subcommittee of WHO. 1999 World Health Organization – International Society of Hypertension guidelines for the management of hypertension. J Hypertens 1999; 17: 151-183.

Guth L, Samaha FJ. Procedure for the histochemical demonstration of actomyosin ATPase. *Exp Neurol.* 1970; 28: 365-367.

Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use and article about therapy or prevention. A. Are the results of the study valid? JAMA 1993; 270: 2598-2601.

Guyton AC, Coleman TG, Cowley AW Jr, Scheel KW, Manning RD Jr, Norman RA Jr. Arterial pressure regulation: overriding dominance of the kidneys in long-term regulation and in hypertension. Am J Med 1972; 52: 584-594.

Gyntelberg F, Meyer J. Relationship between blood pressure and physical fitness, smoking and alcohol consumption in Copenhagen males aged 40-59. Acta Med Scand 1974; 195: 375-380.

Haapanen N, Miilunpalo S, Pasanen M, Oja P, Vuori I. Agreement between questionnaire data and medical records of chronic diseases in middle-aged and elderly Finnish men and women. Am J Epidemiol 1997; 145: 762-769.

Haapanen N, Miilunpalo S, Vuori I, Oja P, Pasanen M. Association of leisure time physical activity with the risk of coronary heart disease, hypertension and diabetes in middle-aged men and women. Int J Epidemiol 1997; 26: 739-747.

Haddy FJ, Pamnani MB. Role of dietary salt in hypertension. J Am Coll Nutr 1995; 14: 428-438.

Hagberg JM, Ferrell RE, Dengel DR, Wilund KR. Exercise training-induced blood pressure and plasma lipid improvements in hypertensives may be genotype dependent. Hypertension 1999; 34: 18-23.

Hagberg JM, Montain SJ, Martin WH, Ehsani AA. Effect of exercise training in 60- to 69-year-old persons with essential hypertension. Am J Cardiol 1989; 64: 348-353.

Hagberg JM, Park JJ, Brown MD. The role of exercise training in the treatment of hypertension. An update. Sports Med 2000; 30: 193-206.

Haglund BJ. A geographical and socioeconomic distribution of high blood pressure and borderline high blood pressure in a Swedish rural county. Scand J Soc Med 1985;13: 53-66.

Halliwill JR. Mechanisms and clinical implications of post-exercise hypotension in humans. Exerc Sports Sci Rev 2001; 29: 65-70.

Hansson JH, Nelson-Williams C, Suzuki H, Schild L, Shimkets R, Lu Y, Canessa C, Iwasaki H, Rossier B, Lifton RP. Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. Nat Genet 1995; 11: 76-82.

Hardman AE. Issues of fractionization of exercise (short vs long bouts). Med Sci Sports Exerc 2001; 33: S421-S427.

Harrap SB. Hypertension: genes versus environment. Lancet 1994; 344: 169-171.

Hartung GH, Kohl HW, Blair SN, Lawrence SJ, Harrist RB. Exercise tolerance and alcohol intake: blood pressure relation. Hypertension 1990; 16: 501-507.

Haskell WL. What to look for in assessing responsiveness to exercise in a health context. Med Sci Sports Exerc 2001; 33 (Suppl): S454-S458.

Hasselstrøm H, Hansen SE, Froberg K, Andersen LB. Physical fitness and physical activity during adolescence as predictors of cardiovascular disease risk in young adulthood. Danish Youth and Sports Study. An Eight-Year Follow-Up Study. Int J Sports Med 2002; 23 (Suppl): S27-S31.

Havlik RJ, Hubert HB, Fabsitz RR, Feinleib M. Weight and hypertension: nutrition and blood pressure control. Ann Intern Med 1983; 98: 855-859.

Hayashi T, Tsumura K, Suematsu C, Okada K, Fujii S, Endo G. Walking to work and the risk for hypertension in men: the Osaka Health Survey. Ann Intern Med 1999; 131: 21-26.

The HDFP Cooperative Group. Race, education, and prevalence of hypertension. Am J Epidemiol 1977; 106: 351-361.

He J, Klag MJ, Whelton PK, Chen JY, Mo JP, Qian MC, Mo PS, He Gq. Migration, blood pressure pattern and hypertension: The Yi Migrant Study. Am J Epidemiol 1991; 134: 1085-1101.

He J, Whelton PK. Epidemiology and prevention of hypertension. Med Clin North Am 1997; 81: 1077-97.

Hedman A, Reneland R, Lithell HO. Alterations in skeletal muscle morphology in glucose tolerant elderly hypertensive men: relationship to development of hypertension and heart rate. J Hypertens 2000; 18: 559-565.

Henrich HA, Romen W, Heimgartner W, Hartung E, Baumer F. Capillary rarefaction characteristic of the skeletal muscle of hypertensive patients. Klin Wochenschr 1988; 66: 54-60.

Hickey N, Mulcahy R, Bourke GJ, Graham I, Wilson-Davis K. Study of coronary risk factors related to physical activity in 15 171 men. Brit Med J 1975; 3: 507-509.

Higashi Y, Sasaki S, Kurisu S, Yoshimizu A, Sasaki N, Matsuura H, Kajiyama G, Oshima T. Regular aerobic exercise augments endothelium-dependent vascular relaxation in normotensive as well as hypertensive subjects. Role of endothelium-derived nitric oxide. Circulation 1999; 100: 1194-1202.

Higashi Y, Sasaki S, Sasaki N, Nakagawa K, Ueda T, Yoshimizu A, Kurisu S, Matsuura H, Kajiyama G, Oshima T. Daily aerobic exercise improves reactive hyperemia in patients with essential hypertension. Hypertension 1999; 33: 591-597.

Hindorff LA, Heckbert SR, Tracy R, Tang Z, Psaty BM, Edwards KL, Siscovick DS, Kronmal RA, Nazar-Stewart V. Angiotensin II type 1 receptor polymorphisms in the cardiovascular health study: relation to blood pressure, ethnicity, and cardiovascular events. Am J Hypertens 2002; 15: 1050-1056.

Hoeymans N, Smit HA, Verkleij H, Kromhout D. Cardiovascular risk factors in relation to educational level in 36 000 men and women in The Netherlands. Eur Heart J 1996; 17: 518-525.

Hong Y, de Faire U, Heller DA, McClearn GE, Pedersen N. Genetic and environmental influences on blood pressure in elderly twins. Hypertension 1994; 24: 663-670.

Hu G, Barengo NC, Tuomilehto J, Lakka TA, Nissinen A, Jousilahti P. Relationship of physical activity and body mass index to the risk of hypertension: a prospective study in Finland. Hypertension 2004; 43: 25-30.

Humerfelt S, Wedervang F. A study of the influence upon blood pressure of marital status, number of children and occupation. Acta Med Scand 1957; 159: 489-497.

Hunt SC, Hasstedt SJ, Kuida H, Stults BM, Hopkins PN, Williams RR. Genetic heritability and common environmental components of resting and stressed blood pressures, lipids, and body mass index in Utah pedigrees and twins. Am J Epidemiol 1989; 129: 625-38.

Hurcomb PG, Wolffsohn JS, Napper GA. Ocular signs of systemic hypertension: a review. Ophtal Physiol Opt 2001; 21: 430-440.

Iliadou A, Lichtenstein P, Morgenstern R, Forsberg L, Svensson R, de Faire U, Martin NG, Pedersen NL. Repeated blood pressure measurements in a sample of Swedish twins: heritabilities and associations with polymorphisms in the renin-angiotensin-aldosterone system. J Hypertens 2002; 20: 1543-1550.

Imazu M. Hypertension and insulin disorders. Curr Hypertens Rep 2002; 4: 477-482.

Imholz BPM, Settels JJ, van der Meiracker AH, Wesseling KH, Wieling W. Non-invasive continuous finger blood pressure measurement during orthostatic stress compared to intra-arterial pressure. Cardiovasc Res 1990; 24: 214-221.

Imholz BPM, van Montfrans GA, Settels JJ, van der Hoeven GMA, Karemaker JM, Wieling W. Continuous non-invasive blood pressure monitoring: reliability of Finapres device during the Valsalva manoeuvre. Cardiovasc Res 1988; 22: 390-397.

Intersalt Co-operative Research Group. Sodium, potassium, body mass, alcohol and blod pressure: the Intersalt Study. J Hypertens 1988; 6 (Suppl): S584-S586.

Jenei Z, Pall D, Katona E, Kakuk G, Polgar P. The epidemiology of hypertension and its associated risk factors in the city of Debrecen, Hungary. Public Health 2002; 116: 138-144.

Jenner DA, Puddey IB, Beilin LJ, Vandongen R. Lifestyle- and occupation-related changes in blood pressure over a six-year period in a cohort of working men. J Hypertens 1988; 6 (suppl 4): S605-S607.

Jennings G, Nelson L, Nestel P, Esler M, Korner P, Burton D, Bazelmans J. The effects of changes in physical activity on major cardiovascular risk factors, hemodynamics, sympathetic function, and glucose utilization in man: a controlled study of four levels of activity. Circulation 1986; 73: 30-40.

Jensen AR. Estimation of the limits of heritability of traits by comparison of monozygotic and dizygotic twins. Proc Natl Acad Sci 1967; 58: 149-156.

Jeunemaitre X, Soubrier F, Kotelevtsev YV, Lifton RP, Williams CS, Charru A, Hunt SC, Hopkins PN, Williams RR, Lalouel JM. Molecular basis of human hypertension: role of angiotensinogen. Cell 1992; 71: 169-180.

Joffres MR, Hamet P, Rabkin SW, Gelskey D, Hogan K, Fodor G. Prevalence, control and awareness of high blood pressure among Canadian adults. Can Med Assoc J 1992; 146: 1997-2005.

Johnson RJ, Herrera-Acosta J, Schreiner GF, Rodriguez-Iturbe B. Mechanisms of disease: subtle acquired renal injury as a mechanism of salt-sensitive hypertension. N Engl J Med 2002; 346: 913-923.

Johnson RJ, Herrera-Acosta J, Schreiner GF, Rodriguez-Iturbe B. Salt-sensitive hypertension. N Engl J Med 2002; 347: 448-449.

Juhlin-Dannfelt A, Frisk-Holmberg M, Karlsson J, Tesch P. Central and peripheral circulation relation to muscle fibre composition in normal and hypertensive men. Clin Sci 1979; 56: 335-340.

Julius S, Valentini M, Palatini P. Overweight and hypertension: a 2-way street? Hypertension 2000; 35: 807-813.

Kannel WB. Blood pressure as a cardiovascular risk factor. JAMA 1996; 275: 1571-1576.

Kannel WB. Elevated systolic blood pressure as a cardiovascular risk factor. Am J Cardiol 2000; 85: 251-255.

Kaplan NM. Systemic hypertension: mechanisms and diagnosis. In: Braunwald E (editor). Heart disease: a textbook of cardiovascular medicine. Third edition. Philadelphia: W.B. Saunders Company; 1988: 819-855.

Kaprio J, Eriksson J, Lehtovirta M, Koskenvuo M, Tuomilehto J. Heritability of leptin levels and the shared genetic effects on body mass index and leptin in adult Finnish twins. Int J Obes 2001; 25: 132-7.

Kaprio J, Koskenvuo M. Genetic and environmental factors in complex diseases: the older Finnish Twin Cohort. Twin Res 2002; 5: 358-365.

Kaprio J, Koskenvuo M, Langinvainio H, Romanov K, Sarna S, Rose RJ. Genetic influences on use and abuse of alcohol: A study of 5638 adult Finnish twin brothers. Alcohol Clin Exp Res 1987; 11: 349-356.

Kaprio J, Koskenvuo M, Sarna S. Cigarette smoking, use of alcohol, and leisure-time physical activity among same-sexed adult male twins.. Prog Clin Biol Res 1981; 69 Pt C: 37-46.

Kaprio J, Sarna S, Koskenvuo M, Rantasalo I. The Finnish Twin Registry: formation and compilation, questionnaire study, zygosity determination procedures and research program. Prog Clin Biol Res 1978; 24B: 179-84.

Katzmarzyk PT, Rankinen T, Pérusse L, Malina RM, Bouchard C. 7-year stability of blood pressure in the Canadian population. Prev Med 2000; 31: 403-409.

Keil JE, Sandifer SH, Loadholt CB, Boyle E Jr. Skin color and education effects on blood pressure. Am J Public Health. 1981; 71: 532-534.

Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. A test of the equal-environment assumption in twin studies of psychiatric illness. Behav Genet 1993; 23: 21-27.

Kendler KS, Gardner CO Jr. Twin studies of adult psychiatric and substance dependence disorders: are they biased by differences in the environmental experiences of monozygotic and dizygotic twins in childhood and adolescence? Psychol Med 1998; 28: 25-633.

Kenney MJ, Seals DR. Postexercise hypotension. Key features, mechanisms, and clinical significance. Hypertension 1993; 22: 653-654.

Keskimäki I, Aro S. Accuracy of data on diagnosis, procedures and accidents in the Finnish hospital discharge register. Int J Health Sciences 1991; 2: 15-21.

Kesäniemi YA, Danforth E Jr, Jensen MD, Kopelman PG, Lefebvre P, Reeder BA. Dose-response issues concerning physical activity and health: an evidence-based symposium. Med Sci Sports Exerc 2001; 33 (Suppl): S351-S358.

Kiiskinen U, Vartiainen E, Puska P, Aromaa A. Long-term cost and life-expectancy consequences of hypertension. J Hypertens 1998; 16: 1103-1112.

Kimura T, Yokoyama T, Matsumura Y, Yoshiike N, Date C, Muramatsu M, Tanaka H. NOS3 genotype-dependent correlation between blood pressure and physical activity. Hypertension 2003; 41: 355-360.

Kingwell BA, Sherrard B, Jennings GL, Dart AM. Four weeks of cycle training increases basal production of nitric oxide from the forearm. Am J Physiol 1997; 272 (Heart Circ Physiol): H1070-H1077.

Kingwell BA, Tran B, Cameron JD, Jennings GL, Dart AM. Enhanced vasodilation to acetylcholine in athletes is associated with lower plasma cholesterol. Am J Physiol 1996; 270 (Heart Circ Physiol): H2008-H2013.

Kinoshita A, Urata H, Tanabe Y, Ikeda M, Tanaka H, Shindo M, Arakawa K. What types of hypertensives respond better to mild exercise therapy? J Hypertens 1988; 6 (suppl 4): S631-S633.

Klatsky AL, Friedman GD, Abraham BS, Gerard MJ. Alcohol consumption and blood pressure: Kaiser Permanente multiphasic health examination data. N Engl J Med 1977; 296: 1194-1200.

Klein R, Klein BE, Moss SE, Wang Q. Blood pressure, hypertension and retinopathy in a population. Trans Am Ophtalmol Soc 1993; 91: 207-222.

Klesges RC, Eck LH, Isbell TR, Fulliton W, Hanson CL. Physical activity, body composition, and blood pressure: a multimethod approach. Med Sci Sports Exerc 1991; 23: 759-765.

Koenig W, Sund M, Fröhlich M, Fischer HG, Löwel H, Döring A, Hutchinson WL, Pepys MB. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation 1999; 99: 237-242.

Komi PV, Viitasalo JH, Havu M, Thorstensson A, Sjodin B, Karlsson J. Skeletal muscle fibres and muscle enzyme activities in monozygous and dizygous twins of both sexes. Acta Physiol Scand 1977; 100: 385-392.

Kool MJF, Struijker-Boudier HA, Wijnen JA, Hoeks APG, van Bortel LM. Effects of diurnal variability and exercise training on properties of large arteries. J Hypertens 1992; 10 (suppl 6): S49-S52.

Koopmans JR, van Doornen LJP, Boomsma DI. Smoking and sports participation. In: Goldbourt U, de Faire U, Berg K (editors). Genetic Factors in Coronary Heart Disease. Kluwer Academic, Dordrecht, Netherlands 1994, pp 217-235.

Koskenvuo M, Kaprio J, Romanov K. Twin studies in metabolic diseases. Ann Med 1992; 24: 379-381.

Kriska AM, Caspersen CJ. Introduction to a collection of physical activity questionnaires. Med Sci Sports Exerc 1997; 29 (Suppl): S5-S9.

Krotkiewski M, Lithell H, Shono N, Wysocki M, Holm G. High blood pressure and muscle morphology/metabolism - causal relationship or only associated factors? Clin Physiol 1998; 18: 203-213.

Kujala UM, Kaprio J, Koskenvuo M. Diabetes in a population-based series of twin pairs discordant for leisure sedentariness. Diabetologia 2000; 43: 259.

Kujala UM, Kaprio J, Koskenvuo M. Modifiable risk factors as predictors of all-cause mortality: the roles of genetics and childhood environment. Am J Epidemiol 2002; 156: 985-993.

Kujala UM, Kaprio J, Sarna S, Koskenvuo M. Relationship of leisure-time physical activity and mortality. The Finnish Twin Cohort. JAMA 1998; 279: 440-4.

Kujala UM, Kaprio J, Taimela S, Sarna S. Prevalence of diabetes, hypertension, and ischemic heart disease in former elite athletes. Metabolism 1994; 43: 1255-1260.

Kujala UM, Kettunen J, Paananen H, Aalto T, Battié MC, Impivaara O, Videman T, Sarna S. Knee osteoarthritis in former runners, soccer players, weight lifters, and shooters. Arthritis Rheum 1995; 38: 539-546.

Kujala UM, Marti P, Kaprio J, Hernelahti M, Tikkanen H, Sarna S. Occurrence of chronic diseases in former top-level athletes. Predominance of benefits, risks or selection effects? Sports Med 2003; 33: 553-561.

Lakka T, Salonen JT. The physical activity questionnaires of the Kuopio Ischemic Heart Disease Study (KIHD). Med Sci Sports Exerc 1997; 29 (Suppl): S46-S58.

Lakka TA, Salonen JT. Moderate to high intensity conditioning leisure time physical activity and high cardiorespiratory fitness associated with reduced plasma fibrinogen in eastern Finnish men. J Clin Epidemiol 1993; 46: 1119-1127.

Lakka TA, Salonen JT. Physical activity and serum lipids: a cross-sectional population study in eastern Finnish men. Am J Epidemiol 1992; 136: 806-818.

Lamonte MJ, Ainsworth BE. Quantifying energy expenditure and physical activity in the context of dose response. Med Sci Sports Exerc 2001; 33 (Suppl): S370-S378.

Lang T, Ducimetière P, Arveiler D, Amouyel P, Cambou JP, Ruidavets JB, Montaye M, Meyer V, Bingham A. Incidence, case fatality, risk factors of acute coronary heart disease and occupational categories in men aged 30-59 in France. Int J Epidemiol 1997; 26: 47-57.

Lange Andersen K, Elvik A. The resting arterial blood pressure in athletes. Acta Med Scand 1956; 153: 367-371.

LaPorte RE, Montoye HJ, Caspersen CJ. Assessment of physical activity in epidemiologic research: problems and prospects. Public Health Rep 1985; 100: 131-146.

Lauderdale DS, Fabsitz R, Meyer JM, Sholinsky P, Ramakrishnan V, Goldberg J. Familial determinants of moderate and intense physical activity: a twin study. Med Sci Sports Exerc 1997; 29: 1062-1068.

Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? I - Analysis of observational data among populations. BMJ 1991; 302: 811-815.

Lefevre J, Philippaerts R, Delvaux K, Thomis M, Claessens AL, Lysens R, Renson R, Vanden Eynde B, Vanreusel B, Beunen G. Relation between cardiovascular risk factors at adult age, and physical activity during youth and adulthood: the Leuven Longitudinal Study on Lifestyle, Fitness and Health. Int J Sports Med 2002; 23 (Suppl): S32-S38.

Lehmann M, Keul J. Häufigkeit der Hypertonie bei 810 männlichen Sportlern. Z Kardiol 1984; 73: 137-141.

Levenstein S, Smith M, Kaplan GA. Psychosocial predictors of hypertension in men and women. Arch Intern Med 2001; 161: 1341-1346.

Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. Ann Intern Med 1988; 108: 7-13.

Levy D, Larson MG, Vasan RS, Kannel WB, Ho KKL. The progression from hypertension to congestive heart failure. JAMA 1996; 275: 1557-1562.

Lifton RP, Dluhy RG, Powers M, Rich GM, Cook S, Ulick S, Lalouel JM. A chimeric 11 β-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. Nature 1992; 355: 262-265.

Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. Cell 2001; 104: 545-556.

Linder L, Kiowski W, Buhler FR, Luscher TF. Indirect evidence for release of endothelium-derived relaxing factor in human forearm in vivo. Blunted response in essential hypertension. Circulation 1990; 81: 1762-1767.

Lissner L, Bengtsson C, Lapidus L, Kristjansson K, Wedel H. Fasting insulin in relation to subsequent blood pressure changes and hypertension in women. Hypertension 1992; 20: 797-801.

Livshits G, Gerber LM. Familial factors of blood pressure and adiposity covariation. Hypertension 2001; 37: 928-935.

Lorentzon M, Lorentzon R, Lerner UH, Nordström P. Calcium sensing receptor gene polymorphism, circulating calcium concentrations and bone mineral density in healthy adolescent girls. Eur J Endocrinol 2001; 144: 257-261.

Luft FC. Molecular genetics of human hypertension. J Hypertens 1998; 16: 1871-1878.

Luft FC. Twins in cardiovascular genetic research. Hypertension 2001; 37: 350-356.

MacAuley D, McCrum EE, Stott G, Evans AE, McRoberts B, Boreham CAG, Sweeney K, Trinick TR. Physical activity, physical fitness, blood pressure, and fibrinogen in the Northern Ireland health and activity survey. J Epidemiol Community Health 1996; 50: 258-63.

MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease, part 1: effects of prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990; 335: 765-774.

MacMahon S. Alcohol consumption and hypertension. Hypertension 1987; 9: 111-121.

MacMahon S. The effects of antihypertensive drug treatment on the incidence of stroke and of coronary heart disease. Clin Exp Hypertens A 1989; 11: 807-823.

Maes HH, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. Behav Genet 1997; 27: 325-351.

Maia JAR, Thomis M, Beunen G. Genetic factors in physical activity levels: a twin study. Am J Prev Med 2002; 23 (2S): 87-91.

Mancia G. Björn Folkow Award Lecture. The sympathetic nervous system in hypertension. J Hypertens 1997; 15: 1553-1565.

Manunta P, Cusi D, Barlassina C, Righetti M, Lanzani C, D'Amico M, Buzzi L, Citterio L, Stella P, Rivera R, Bianchi G. α-adducin polymorphisms and renal sodium handling in essential hypertensive patients. Kidney Int 1998; 53: 1471-1478.

Marigliano A, Tedde R, Sechi LA, Pala A, Pisanu G, Pacifico A. Insulinemia and blood pressure. Relationships in patients with primary and secondary hypertension, and with or without glucose metabolism impairment. Am J Hypertens 1990; 3: 521-526.

Marmot MG, Elliott P, Shipley MJ, Dyer AR, Ueshima HU, Beevers DG, Stamler R, Kesteloot H, Rose G, Stamler J. Alcohol and blood pressure: the INTERSALT study. BMJ 1994; 308: 1263-1267.

Marshall EC, Malinovsky VE. Hypertension and the eye: applications of the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. J Am Optom Assoc 1998; 69: 281-291.

Martin WH, Ogawa T, Kohrt WM, Malley MT, Korte E, Kieffer PS, Schechtman KB. Effects of aging, gender, and physical training on peripheral vascular function. Circulation 1991; 84: 654-664.

Masaki KH, Curb D, Chiu D, Petrovitch H, Rodriguez BL. Association of body mass index with blood pressure in elderly Japanese American men. The Honolulu Heart Program. Hypertension 1997; 29: 673-677.

Melander O. From linkage to genes in human hypertension. J Hypertens 2002; 20: 2135-2138.

Mensink GBM, Heerstrass DW, Neppelenbroek SE, Schuit AJ, Bellach B. Intensity, duration, and frequency of physical activity and coronary risk factors. Med Sci Sports Exerc 1997; 29: 1192-1198.

Meredith IT, Friberg P, Jennings GL, Dewar EM, Fazio VA, Lambert GW, Esler MD. Exercise training lowers resting renal but not cardiac sympathetic activity in humans. Hypertension 1991; 18: 575-582.

Meredith IT, Jennings GL, Esler MD, Dewar EM, Bruce AM, Fazio VA, Korner PI. Time-course of the antihypertensive and autonomic effects of regular endurance exercise in human subjects. J Hypertens 1990; 8: 859-866.

Miall WE, Oldham PD. Factors influencing arterial blood pressure in the general population. Clin Sci 1958; 17: 409-444.

Midgley JP, Matthew AG, Greenwood CM, Logan AG. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. JAMA 1996; 275: 1590-1597.

Mongeau JG, Biron P, Sing CF. The influence of genetics and household environment upon the variability of normal blood pressure: the Montreal Adoption Survey. Clin Exper Hypertens 1986; 8: 653-660.

Montoye HJ, Metzner HL, Keller JB, Johnson BC, Epstein FH. Habitual physical activity and blood pressure. Med Sci Sports 1972; 4: 175-181.

Moore RD, Levine DM, Southard J, Entwisle G, Shapiro S. Alcohol consumption and blood pressure in the 1982 Maryland Hypertension Survey. Am J Hypertens 1990; 3: 1-7.

Morris JN. Occupation and coronary heart disease. Arch Intern Med 1959; 104: 903-907.

Mune T, Roberson FM, Nikkilä H, Agarwal AK, White PC. Human hypertension caused by mutations in the kidney isozyme of 11 β-hydroxysteroid dehydrogenase. Nat Genet 1995; 10: 394-399.

Neale MC, Cardon LR. Methodology for genetic studies of twins and families. Kluwer Academic, Dordrecht, The Netherlands, 1992.

Neale MC. Mx: statistical modelling [computer program and manual]. 5th edition. Richmond (VA): Medical College of Virginia, Department of Psychiatry, 1999.

Nelson L, Esler MD, Jennings GL, Korner PI. Effect of changing levels of physical activity on blood pressure and haemodynamics in essential hypertension. Lancet 1986; 2: 473-476.

Niedhammer I, Goldberg M, Leclerc A, David S, Bugel I, Landre MF. Psychosocial work environment and cardiovascular risk factors in an occupational cohort in France. J Epidemiol Community Health 1998; 52: 93-100.

O'Donnell CJ, Lindpaintner K, Larson MG, Rao VS, Ordovas JM, Schaefer EJ, Myers RH, Levy D. Evidence for association and genetic linkage of the angiotensin-converting enzyme locus with hypertension and blood pressure in men but not women in the Framingham Heart Study. Circulation 1998; 97: 1766-1772.

O'Sullivan SE, Bell C. The effects of exercise and training on human cardiovascular reflex control. J Autonom Nerv Syst 2000; 81: 16-24.

Paffenbarger RS Jr, Blair SN, Lee I, Hyde RT. Measurement of physical activity to assess health effects in free-living populations. Med Sci Sports Exerc 1993; 25: 60-70.

Paffenbarger RS Jr, Jung DL, Leung RW, Hyde RT. Physical activity and hypertension: an epidemiological view. Ann Med 1991; 23: 319-327.

Paffenbarger RS Jr, Wing AL, Hyde RT, Jung DL. Physical activity and incidence of hypertension in college alumni. Am J Epidemiol 1983; 117: 245-257.

Palatini P, Graniero GR, Mormino P, Nicolosi L, Mos L, Visentin P, Pessina AC. Relation between physical training and ambulatory blood pressure in stage I hypertensive subjects. Results of the HARVEST trial. Circulation 1994; 90: 2870-2876.

Panza JA, Quyyumi AA, Brush JE Jr, Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. N Engl J Med 1990; 323: 22-27.

Parati G, Casadei R, Groppelli A, Di Rienzo M, Mancia G. Comparison of finger and intra-arterial blood pressure monitoring at rest and during laboratory testing. Hypertension 1989; 13: 647-655.

Pereira MA, Folsom AR, McGovern PG, Carpenter M, Arnett DK, Liao D, Szklo M, Hutchinson RG. Physical activity and incident hypertension in black and white adults: the Atherosclerosis Risk in Communities Study. Prev Med 1999; 28: 304-312.

Pérusse L, Leblanc C, Bouchard C. Inter-generation transmission of physical fitness in the Canadian population. Can J Sport Sci 1988; 13: 8-14.

Pérusse L, Tremblay A, Leblanc C, Bouchard C. Genetic and environmental influences on level of habitual physical activity and exercise participation. Am J Epidemiol 1989; 129: 1012-1022.

Pescatello LS, Fargo AE, Leach CN Jr, Scherzer HH. Short-term effect of dynamic exercise on arterial blood pressure. Circulation 1991; 83: 1557-1561.

Pette D, Staron RS. Myosin isoforms, muscle fiber types, and transitions. Microsc Res Tech 2000; 50: 500-509.

Pickering GW. The nature of essential hypertension. Lancet 1959; 2: 1027-1028.

Pihl E, Jürimäe T, Kaasik T. Coronary heart disease risk factors in middle-aged former top-level athletes. Scand J Med Sci Sports 1998; 8: 229-235.

Platt R. Heredity in hypertension Q J Med 1947; 16: 111-133.

Pollare T, Lithell H, Berne C. Insulin resistance is a characteristic feature of primary hypertension independent of obesity. Metabolism 1990; 39: 167-174.

Posthuma D, Beem AL, de Geus EJC, van Baal GCM, von Hjelmborg JB, Iachine I, Boomsma DI. Theory and practice in quantitative genetics. Twin Res 2003; 6: 361-376.

Potter JF, Beevers DG. Pressor effect of alcohol in hypertension. Lancet 1984; 1: 119-122.

Powell KE, Thompson PD, Caspersen CJ, Kendrick JS. Physical activity and the incidence of coronary heart disease. Annu Rev Public Health 1987; 8: 253-287.

Pyörälä K, Karvonen MJ, Taskinen P, Takkunen J, Kyrönseppä H, Peltokallio P. Cardiovascular studies on former endurance athletes. Am J Cardiol 1967; 20: 191-205.

Raab W, Krzywanek HJ. Cardiovascular sympathetic tone and stress response related to personality patterns and exercise habits. A potential cardiac risk and screening test. Am J Cardiol 1965; 16: 42-53.

Randin D, Vollenweider P, Tappy Luc, Jequier E, Nicod P, Scherrer U. Suppression of alcohol-induce hypertension by dexamethasone. N Engl J Med 1995; 332: 1733-1737.

Rankinen T, Pérusse L, Rauramaa R, Rivera MA, Wolfarth B, Bouchard C. The human gene map for performance and health-related fitness phenotypes: the 2003 update. Med Sci Sports Exerc 2004; 36: 1451-1469.

Rauramaa R, Väisänen SB, Rankinen T, Penttilä IM, Saarikoski S, Tuomilehto J, Nissinen A. Inverse relation of physical activity and apolipoprotein AI to blood pressure in elderly women. Med Sci Sports Exerc 1995; 27: 164-169.

Rauramaa R, Kuhanen R, Lakka TA, Väisänen SB, Halonen P, Alén M, Rankinen T, Bouchard C. Physical exercise and blood pressure with reference to the angiotensinogen M235T polymorphism. Physiol Genomics 2002; 10: 71-77.

Reaven PD, Barrett-Connor E, Edelstein S. Relation between leisure-time physical activity and blood pressure in older women. Circulation 1991; 83: 559-565.

Reaven GM. Insulin resistance/compensatory hyperinsulinemia, essential hypertension, and cardiovascular disease. J Clin Endocrinol Metab 2003; 88: 2399-2403.

Reiser PJ, Moss RL, Giulian GG, Greaser ML. Shortening velocity in single fibers from adult rabbit soleus muscles is correlated with myosin heavy chain composition. J Biol Chem 1985; 260: 9077-9080.

Rice T, An P, Gagnon J, Leon AS, Skinner JS, Wilmore JH, Bouchard C, Rao DC. Heritability of HR and BP response to exercise training in the HERITAGE Family Study. Med Sci Sports Exerc 2002; 34: 972-979.

Rice T, Vogler GP, Perusse L, Bouchard C, Rao DC. Cardiovascular risk factors in a French Canadian population: resolution of genetic and familial environmental effects on blood pressure using twins, adoptees, and extensive information on environmental correlates. Genet Epidemiol 1989; 6: 571-588.

Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342: 836-843.

Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001; 103: 1813-1818.

Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch V, Martin M. The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. N Engl J Med 1989; 321: 580-585.

Rocchini AP. Obesity hypertension. Am J Hypertens 2002; 15: 50S-52S.

Rogers MA, Evans WJ. Changes in skeletal muscle with aging: effects of exercise training. Exerc Sport Sci Rev 1993; 21: 65-102.

Ropponen A, Levälahti E, Simonen R, Videman T, Battié MC. Repeatability of lifetime exercise reporting. Scand J Med Sci Sports 2001; 11: 185-192.

Rosito GA, Fuchs FD, Duncan BB. Dose-dependent biphasic effect of ethanol on 24-h blood pressure in normotensive subjects. Am J Hypertens 1999; 12: 236-240.

Rosmond R, Dallman MF, Björntorp P. Stress-related cortisol secretion in men: relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities. J Clin Endocrinol Metab 1998; 83: 1853-1859.

Rosmond R, Holm G, Björntorp P. Food-induced cortisol secretion in relation to anthropometric, metabolic and haemodynamic variables in men. Int J Obes Relat Metab Disord 2000; 24: 416-422.

van Rossum CT, van de Mheen H, Witteman JC, Hofman A, Mackenbach JP, Grobbee DE. Prevalence, treatment, and control of hypertension by sociodemographic factors among the Dutch elderly. Hypertension 2000; 35: 814-821.

Rumantir MS, Vaz M, Jennings GL, Collier G, Kaye DM, Seals DR, Wiesner GH, Brunner-La Rocca HP, Esler MD. Neural mechanisms in human obesity-related hypertension. J Hypertens 1999; 17: 1125-1133.

Rutherford PA. Genetic influences in human hypertension. 2003; 21: 19-22.

Räikkönen K, Matthews KA, Kuller LH. Trajectory of psychological risk and incident hypertension in middle-aged women. Hypertension 2001; 38: 798-802.

Sallis JF, Patterson TL, Buono MJ, Atkins CJ, Nader PR. Aggregation of physical activity habits in Mexican-American and Anglo families. J Behav Med 1988; 11: 31-41.

Salonen JT, Lakka TA. Assessment of physical activity in population studies – validity and consistency of the methods in the Kuopio ischemic heart disease risk factor study. Scand J Sports Sci 1987; 9: 89-95.

Saltin B, Grimby G. Physiological analysis of middle-aged and old former athletes. Comparison with still active athletes of the same ages. Circulation 1968; 38: 1104-1115.

Saltin B. Hemodynamic adaptations to exercise. Am J Cardiol 1985; 55: 42D-47D.

Saltin B, Gollnick PD. Skeletal muscle adaptability, significance for metabolism and performance. In: Peachey LD, ed. *Handbook of Physiology.* Baltimore, United States: Williams and Wilkins; 1983:555-631.

Samani NJ. Genome scans for hypertension and blood pressure regulation. Am J Hypertens 2003; 16: 167-171.

Sarna S, Sahi T, Koskenvuo M, Kaprio J. Increased life expectancy of world class male athletes. Med Sci Sports Exerc 1993; 25: 237-244.

Saunders JB, Beevers DG, Paton A. Alcohol-induced hypertension. Lancet 1981; 2: 653-656.

Schork NJ, Weder AB, Trevisan M, Laurenzi M. The contribution of pleiotropy to blood pressure and body-mass index variation: The Gubbio Study. Am J Hum Genet 1994; 54: 361-373.

Seals DR, Reiling MJ. Effect of regular exercise on 24-hour arterial pressure in older hypertensive humans. Hypertension 1991; 18: 583-592.

Senitko AN, Charkoudian N, Halliwill JR. Influence of endurance exercise training status and gender on postexercise hypotension. J Appl Physiol 2002; 92: 2368-2374.

Shamiss A, Carroll J, Rosenthal T. Insulin resistance in secondary hypertension. Am J Hypertens 1992; 5: 26-28.

Shimkets RA, Warnock DG, Bositis CM, Nelson-Williams C, Hansson JH, Schambelan M, Gill JR Jr, Ulick S, Milora RV, Findling JW, Canessa CM, Rossier BC, Liftorn RP. Liddle's syndrome: heritable human hypertension caused by mutations in the β-subunit of the epithelial sodium channel. Cell 1994; 79: 407-414.

Siffert W, Rosskopf D, Siffert G, Busch S, Moritz A, Erbel R, Sharma AM, Ritz E, Jakobs KH, Horsthemke B. Association of a human G-protein β3-subunit variant with hypertension. Nat Genet 1998; 18: 45-48.

Simoneau J-A, Bouchard C. Genetic determinism of fiber type proportion in human skeletal muscle. FASEB J 1995; 9: 1091-1095.

Simonen RL, Pérusse L, Rankinen T, Rice T, Rao DC, Bouchard C. Familial aggregation of physical activity levels in the Québec family study. Med Sci Sports Exerc 2002; 34: 1137-1142.

Simonen RL, Rankinen T, Pérusse L, Rice T, Rao DC, Chagnon Y, Bouchard C. Genome-wide linkage scan for physical activity levels in the Quebec Family Study. Med Sci Sports Exerc 2003; 35: 1355-1359.

Simonen RL, Rankinen T, Pérusse L, Leon AS, Skinner JS, Wilmore JH, Rao DC, Bouchard C. A dopamine D2 receptor gene polymorphism and physical activity in two family studies. Physiol Behav 2003; 78: 751-757.

Skarfors ET, Lithell HO, Selinus I. Risk factors for the development of hypertension: a 10-year longitudinal study in middle-aged men. J Hypertens 1991; 9: 217-223.

Slattery ML, Bishop T, French TK, Hunt SC, Meikle AW, Williams RR. Lifestyle and blood pressure levels in male twins in Utah. Genet Epidemiol 1988; 5: 277-287.

Smerdu V, Karsch-Mizrachi I, Campione M, Leinwand L, Schiaffino S. Type IIx myosin heavy chain transcripts are expressed in type IIb fibers of human skeletal muscle. Am J Physiol 1994; 267: C1723-C1728.

Smithies O, Hyung-Suk K, Takahashi N, Edgell MH. Importance of quantitative genetic variations in the etiology of hypertension. Kidney Int 2000; 58: 2265-2280.

Snieder H, Hayward CS, Perks U, Kelly RP, Kelly PJ, Spector TD. Heritability of central systolic pressure augmentation. A twin study. Hypertension 2000; 35: 574-579.

Sobngwi E, Mbanya JCN, Unwin NC, Kengne AP, Fezeu L, Minkoulou EM, Aspray TJ, Alberti KGMM. Physical activity and its relationship with obesity, hypertension and diabetes in urban and rural Cameroon. Int J Obesity 2002; 26: 1009-1016.

Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease. Hypertension 2001; 37: 1053-1059.

Sowers JR. Insulin resistance and hypertension. Am J Physiol Heart Circ Physiol 2004; 286: H1597-H1602.

Spangenburg EE, Booth FW. Molecular regulation of individual skeletal muscle fibre types. Acta Physiol Scand 2003; 178: 413-424.

Staessen JA, Fagard R, Amery A. Life style as a determinant of blood pressure in the general population. Am J Hypertens 1994; 7: 685-694.

Staessen JA, Gasowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, Coope J, Ekbom T, Gueyffier F, Liu L, Kerlikowske K, Pocock S, Fagard RH. Risks of untreated and treated isolated hypertension in the elderly: meta-analysis of outcome trials. Lancet 2000; 355: 865-872.

Staessen JA, Kuznetsova T, Wang JG, Emelianov D, Vlietinck R, Fagard R. M235T angiotensinogen gene polymorphism and cardiovascular renal risk. J Hypertens 1999; 17: 9-17.

Staessen JA, Wang JG, Brand E, Barlassina C, Birkenhager WH, Herrmann SM, Fagard R, Tizzoni L, Bianchi G. Effects of three candidate genes on prevalence and incidence of hypertension in a Caucasian population. J Hypertens 2001; 19: 1349-1358.

Stamler J, Caggiula AW, Grandits GA. Relation of body mass and alcohol, nutrient, fiber, and caffeine intakes to blood pressure in the special intervention and usual care groups in the Multiple Risk Factor Intervention Trial. Am J Clin Nutr 1997; 65 (Suppl): 338S-65S.

Stamler J, Liu K, Ruth KJ, Pryer J, Greenland P. Eight-year blood pressure change in middle-aged men: relationship to multiple nutrients. Hypertension 2002; 39: 1000-1006.

Stamler R, Stamler J, Riedlinger WF, Algera G, Roberts RH. Weight and blood pressure: findings in hypertension screening of 1 million Americans. JAMA 1978; 240: 1607-1610.

Stankovic A, Zivkovic M, Alavantic D. Angiotensin I-converting enzyme gene polymorphism in a Serbian population: a gender-specific association with hypertension. Scand J Clin Lab Invest 2002; 62: 469-476.

Stankovic A, Zivkovic M, Glisic S, Alavantic D. Angiotensin II type 1 receptor gene polymorphism and essential hypertension in Serbian population. Clin Chim Acta 2003: 327: 181-185.

Staron RS, Pette D. Correlation between myofibrillar ATPase activity and myosin heavy chain composition in rabbit muscle fibers. Histochemistry 1986; 86: 19-23.

Statistics Finland. Causes of death 2002. Terveys 2003; 2.

Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD. Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. J Clin Invest 1996; 97: 2601-2610.

Stender M, Hense H, Döring A, Keil U. Physical activity at work and cardiovascular disease risk: results from the MONICA Augsburg Study. Int J Epidemiol 1993; 22: 644-650.

Stevenson ET, Davy KP, Jones PP, Desouza CA. Blood pressure risk factors in healthy postmenopausal women: physical activity and hormone replacement. J Appl Physiol 1997; 82: 652-660.

Svedenhag J, Martinsson A, Ekblom B, Hjemdahl P. Altered cardiovascular responsiveness to adrenaline in endurance-trained subjects. Acta Physiol Scand 1986; 126: 539-550.

Talmadge RJ, Roy RR, Edgerton VR. Distribution of myosin heavy chain isoforms in non-weight-bearing rat soleus muscle fibers. J Appl Physiol 1996; 81: 2540-2546.

Tanaka H, Davy KP, Seals DR. Cardiopulmonary baroreflex inhibition of sympathetic nerve activity is preserved with age in healthy humans. J Physiol 1999; 515: 249-254.

Tanaka H, Reiling MJ, Seals DR. Regular walking increases peak limb vasodilatory capacity of older hypertensive humans: implications for arterial structure. J Hypertens 1998; 16: 423-428.

Thadhani R, Camargo CA, Stampfer MJ, Curhan GC, Willett WC, Rimm EB. Prospective study of moderate alcohol consumption and risk of hypertension in young women. Arch Intern Med 2002; 162: 569-574.

Thompson PD, Crouse SF, Goodpaster B, Kelley D, Moyna N, Pescatello L. The acute versus the chronic response to exercise. Med Sci Sports Exerc 2001; 33 (Suppl): S438-S445.

Tikkanen HO, Hämäläinen E, Härkönen M. Significance of skeletal muscle properties on fitness, long-term physical training and serum lipids. Atherosclerosis 1999; 142: 367-378.

Tikkanen HO, Hämäläinen E, Sarna S, Adlercreutz H, Härkönen M. Associations between skeletal muscle properties, physical fitness, physical activity and coronary heart disease risk factors in men. Atherosclerosis. 1998; 137: 377-389.

Tikkanen HO, Härkönen M, Näveri H, Hämäläinen E, Elovainio R, Sarna S, Frick MH. Relationship of skeletal muscle fiber type to serum high density lipoprotein cholesterol and apolipoprotein A-I levels. Atherosclerosis 1991; 90: 49-57.

Timmermann B, Mo R, Luft FC, Gerdts E, Busjahn A, Omvik P, Li GH, Schuster H, Wienker TF, Hoehe MR, Lund-Johansen P. β_2-adrenoceptor genetic variation is associated with genetic propensity to essential hypertension: The Bergen Blood Pressure Study. Kidney Int 1998; 53: 1455-1460.

Toft I, Bønaa KH, Lindal S, Berg TJ, Jenssen T. Population-based study of the relationship among muscle morphology, insulin action, and hypertension. Am J Hypertens 1999; 12: 1209-1216.

Trials of Hypertension Prevention Collaborative Research Group. The effects of non-pharmacologic interventions on blood pressure of persons with high normal levels: results of the Trials of Hypertension Prevention, Phase I. JAMA 1992; 267: 1213-1220.

Tsevat J, Weinstein MC, Williams LW, Tosteson ANA, Goldman L. Expected gains in life-expectancy from various coronary heart disease risk factor modifications. Circulation 1991; 83: 1194-1201.

Tsutsumi A, Kayaba K, Tsutsumi K, Igarashi M. Association between job strain and prevalence of hypertension: a cross sectional analysis in a Japanese working population with a wide range of occupations: the Jichi Medical School cohort study. Occup Environ Med 2001; 58: 367-373.

Tuck MI, Sowers J, Dornfield L, Kledzik G, Maxwell M. The effect of weight reduction on blood pressure plasma renin activity and plasma aldosterone level in obese patients. N Engl J Med 1981; 304: 930-933.

Twisk JWR. Physical activity guidelines for children and adolescents: a critical review. Sports Med 2001; 31: 617-627.

Twisk JWR, Kemper HCG, van Mechelen W. Prediction of cardiovascular disease risk factors later in life by physical activity and physical fitness in youth: introduction. Int J Sports Med 2002; 23 (Suppl): S5-S7.

Twisk JWR, Kemper HCG, van Mechelen W. The relationship between physical fitness and physical activity during adolescence and cardiovascular disease risk factors at adult age. The Amsterdam Growth and Health Longitudinal Study. Int J Sports Med 2002; 23 (Suppl): S8-S14.

Twisk JWR, Kemper HCG, van Mechelen W. Prediction of cardiovascular disease risk factors later in life by physical activity and physical fitness in youth: general comments and conclusions. Int J Sports Med 2002; 23 (Suppl): S44-S49.

Urata H, Tanabe Y, Kiyonaga A, Ikeda M, Tanaka H, Shindo M, Arakawa K. Antihypertensive and volume-depleting effects of mild exercise on essential hypertension. Hypertension 1987; 9: 245-252.

Valderrábano F, Gómez-Campderá F, Jones E. Hypertension as cause of end-stage renal disease: lessons from international registries. Kidney Int Suppl 1998: 54 (Suppl 68): S-60-S-66.

Vinck WJ, Fagard RH, Loos R, Vlietinck R. The impact of genetic and environmental influences on blood pressure variance across age-groups. J Hypertens 2001; 19: 1007-1013.

Wamala SP, Wolk A, Orth-Gomer K. Determinants of obesity in relation to socioeconomic status among middle-aged Swedish women. Prev Med 1997;26 (Suppl 1): 734-744.

Wareham NJ, Wong M, Hennings S, Mitchell J, Rennie K, Cruickshank K, Day NE. Quantifying the association between habitual energy expenditure and blood pressure. Int J Epidemiol 2000; 29: 655-660.

Weinberger MH. Salt sensitivity of blood pressure in humans. Hypertension 1996; 27 481-490.

Whelton PK, He J, Cutler JA, Brancanti FL, Appel LJ, Follmann D, Klag MJ. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. JAMA 1997; 277: 1624-1632.

Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure:a meta-analysis of randomized, controlled trials. Ann Intern Med 2002; 136: 493-503.

Whitlock G, Clark T, Vander Hoorn S, Rodgers A, Jackson R, Norton R, MacMahon S. Random errors in the measurement of 10 cardiovascular risk factors. Eur J Epidemiol 2001; 17: 907-909.

Willerman L, Plomin R. Activity level in children and their parents. Child Dev 1973; 44: 854-858.

Williams CJ, Christian JC, Norton JA. TWINAN90: A Fortran program for conducting ANOVA-based and likelihood-based analysis of twin data. Comput Meth Programs Biomed. 1992; 38: 167-176.

Williams PT. Relationships of heart disease risk factors to exercise quantity and intensity. Arch Intern Med 1998; 158: 237-245.

Wilson PWF, Paffenbarger RS, Morris JN, Havlik RJ. Assessment methods for physical activity and physical fitness in population studies: report of a NHLBI workshop. Am Heart J 1986; 111: 1177-1192.

Xin X, He J, Frontini MG, Ogden LG, Motsamai OI, Whelton PK. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension 2001; 38: 1112-1117.

Xu X, Nui T, Christiani DC, Weiss ST, Zhou Y, Chen C, Yang J, Fang Z, Jiang Z, Liang W, Zhang F. Environmental and occupational determinants of blood pressure in rural communities in China. Ann Epidemiol 1997; 7: 95-106.

Yang YC, Huang SC, Wu JS, Chang CJ. Community-based study on the relationship between physical activity and hypertension. J Formos Med Assoc 1996; 95: 110-118.

Young DR, Haskell WL, Jatulis DE, Fortmann SP. Associations between changes in physical activity and risk factors for coronary heart disease in a community-based sample of men and women: the Stanford Five-City Project. Am J Epidemiol 1993; 138: 205-216.

Young JH, Klag MJ, Muntner P, Whyte JL, Pahor M, Coresh J. Blood pressure and decline in kidney function: findings from the Systolic Hypertension in the Elderly Program (SHEP). J Am Soc Nephrol 2002; 13: 2776-2782.

Zavaroni I, Mazza S, Dall'Aglio E, Gasparini P, Passeri M, Reaven GM. Prevalence of hyperinsulinaemia in patients with high blood pressure. J Intern Med 1992; 231: 235-240.

Zeppilli P, Vannicelli R, Santini C, Dello Russo A, Picani C, Palmieri V, Cameli S, Corsetti R, Pietrangeli L. Echocardiographic size of conductance vessels in athletes and sedentary people. Int J Sports Med 1995; 16: 38-44.

Zhang B, Sakai T, Miura S, Kiyonaga A, Tanaka H, Shindo M, Saku K. Association of angiotensin-converting enzyme gene polymorphism with the depressor response to mild exercise therapy in patients with mild to moderate essential hypertension. Clin Genet 2002; 62: 328-333.