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ABSTRACT

Peripheral arterial disease (PAD) is a treacherous disease because it remains asymptomatic for so long. As PAD progresses, it may lead to classical intermittent claudication and critical limb ischemia. The majority of PAD patients die of cardiac and cerebrovascular-related events. The 5-year mortality of PAD patient is 15-30%.

The ankle-brachial index (ABI) has been acknowledged as a valid, non-invasive and simple instrument for detecting PAD in lower extremities and can be used in a community-based primary care setting. The most commonly used ABI threshold is ≤ 0.90 based on studies reporting over 90% sensitivity and specificity to detect PAD defined as >50% arterial stenosis in lower-extremity angiography. The major cause of PAD is atherosclerosis. Therefore, ABI has emerged as a useful tool also for cardiovascular risk stratification. Several recent studies have shown that even persons with borderline ABI (ABI 0.91-1.00) have increased rates of cardiovascular morbidity and mortality.

The Harmonica Project is a community-based survey designed to evaluate CVD risk factors among the residents of the rural town of Harjavalta in Finland, in 2005 and 2006. ABI and classical cardiovascular risk factors were measured from subjects with high cardiovascular risk (n = 972). Participants with previously diagnosed diabetes, cardiovascular or renal disease were excluded. Generic health questionnaires were filled in by all the subjects, including IIEF-5 (Index of Erectile Function short form), leisure-time physical activity and Beck´s Depression Inventory. The study subjects with borderline ABI (0.91 - 1.00) at baseline were invited for a follow-up visit in 2012. A modified questionnaire, laboratory tests and ABI measurements were repeated for them.

At baseline, the prevalence of PAD and borderline ABI were, 5% and 20%, respectively. In men, short stature was associated with higher prevalence of PAD and lower ABI values compared to taller men.

Erectile dysfunction was significantly associated with lower ABI values among men over 60 years old. Therefore, in primary care setting, physicians should consider measuring ABI in elderly men suffering from ED, especially if markedly elevated cardiovascular risk factors are present.

Our study also revealed the link between diastolic blood pressure and erectile dysfunction. Our results support the optimum diastolic blood pressure of 90 mmHg for erectile function.

In our longitudinal study, physical activity was significantly associated with improved ABI values among men and women with borderline ABI. Our results suggest that it might be beneficial to pay more attention to patients with borderline ABI and offer them cardiovascular intervention and emphasizing the role of exercise, without forgetting the importance of smoking cessation.

Keywords: peripheral arterial disease, ankle brachial-index, erectile dysfunction, physical activity, height, hypertension

Arto Heikkilä
Perifeerinen valtimotauti ja erektiohäiriö perusterveydenhuollossa
Turun yliopisto, Lääketieteellinen tiedekunta, Yleislääketiede; Turun kliininen tohtoriohjelma; Satakunnan keskussairaala, Kirurgian klinikka; Keski-Satakunnan terveydenhuollon kuntayhtymä, Harjavalta. Annales Universitatis Turkuensis, Turku, Suomi 2018

TIIVISTELMÄ

Perifeerinen valtimotauti eli alaraajojen tukkiva valtimotauti on pitkään salakavalan oireeton. Taudin edetessä oireina saattaa kehittyä klassista katkokävelyä, leposärkyä ja haavaumia. Taudin ennuste on huono; viiden vuoden kuluessa 15-30 % potilaista kuolee pääasiassa sydän- ja verisuonisairauksiin.

Nilkka-olkavarsipainesuhde (ankle-brachial index, ABI) -mittaus on helposti toteutettava, edullinen, kajoamaton ja laadukas menetelmä alaraajojen valtimoverenkierron arviointiin ja se soveltuu hyvin perusterveydenhuollon käyttöön. Yleisin käytetty raja-arvo nilkka-olkavarsipainesuhteelle on ≤ 0.90, joka tunnistaa perifeerisen valtimotaudin yli 90 %:n herkkyydellä ja tarkkuudella, kun määritelmänä on >50%:n ahtauma alaraajavaltimoiden varjoainekuvauksessa. Valtimonkovettumatauti rajoittuu harvoin pelkästään alaraajavaltimoihin ja nilkka-olkavarsipainesuhde onkin todettu olevan käyttökelpoinen menetelmä myös yleisen valtimotautiriskin arvioinnissa. Myös raja-arvoisten nilkka-olkavarsipainesuhteiden (ABI 0.91-1.00) on uusissa tutkimuksissa todettu lisäävän potilaan valtimotautikuolleisuutta.

Kokemäen jokilaakson valtimotautien seulontaprojekti toteutettiin Harjavallassa vuosina 2005 – 2006. Kaikilta korkean riskin henkilöiltä määritettiin perinteiset valtimotaudin riskitekijät ja mitattiin nilkka-olkavarsipainesuhde (n = 972). Henkilöillä, joilla oli aikaisemmin todettu valtimotauti, diabetes tai munuaisten vajaatoiminta, suljettiin tutkimuksen ulkopuolelle. Lisäksi kyselykaavakkeilla selvitettiin mm. erektiohäiriöitä (Index of Erectile Function short form -kaavake), liikuntatottumuksia ja masennusoireita (Beck´s Depression Inventory -kaavake). Tutkitut, joilla todettiin seulonnassa perifeerinen valtimotauti (ABI ≤0.90) tai raja-arvoinen nilkka-olkavarsipainesuhde (ABI 0.91-1.00), kutsuttiin vuonna 2012 seurantakäynneille, joissa seulontatutkimukset toistettiin.

Poikkileikkaustutkimuksessa 5%:lla tutkituista oli perifeerinen valtimotauti ja 20%:lla raja-arvoinen nilkka-olkavarsipainesuhde. Lyhyillä miehillä todettiin alhaisemmat ABI-arvot ja enemmän perifeeristä valtimotautia kuin pitkillä miehillä. Naisilla ei vastaavaa yhteyttä todettu.

Alhainen nilkka-olkavarsipainesuhde liittyi lisääntyneeseen erektiohäiriön riskiin yli 60 vuotiailla miehillä. Perusterveydenhuollossa lääkärin tulisikin harkita nilkka-olkavarsipainesuhteen määrittämistä erektiohäiriöisiltä vanhemmilta miehiltä mahdollisen oireettoman perifeerisen valtimotaudin toteamiseksi, varsinkin jos heillä todetaan merkittävästi kohonneita valtimoriskitekijöitä. Lisäksi aineistossamme löydettiin diastolisen verenpaineen ja erektiohäiriön välinen yhteys. Optimaalinen diastolinen verenpaine erektioon vaikuttaisi olevan 90 mmHg.

Seurantatutkimuksessamme saatiin selville, että liikunta vaikuttaa merkittävästi nilkka-olkavarsipainesuhteen kehitykseen. Runsaasti liikuntaa harrastavilla naisilla ja miehillä raja-arvoiset nilkka-olkavarsipainesuhteet (ABI 0.91-1.00) paranivat tilastollisesti merkitsevästi seitsemän vuoden seurannassa. Jatkossa tulisikin kiinnittää huomiota näiden raja-arvoisten potilaiden kardiovaskulaariseen interventioon liikunnan lisäämisen kautta, unohtamatta tupakonnin lopettamisen merkitystä.

Avainsanat: perifeerinen valtimotauti, erektiohäiriö, nilkka-olkavarsipainesuhde, liikunta, pituus, verenpainetauti.

TABLE OF CONTENTS

ABBREVIATIONS

ABI	Ankle-brachial index
ADP	Dorsalis pedis artery
AHA	American Heart Association
ATP	Tibial posterior artery
CAD	Coronary artery disease
CBVD	Cerebrovascular disease
BDI	Beck´s Depression Inventory
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CLI	Critical limb ischemia
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
ED	Erectile dysfunction
FINDRISK	Finnish Diabetes Risk Score
HDL-C	High-density lipoprotein cholesterol
IFG	Impaired fasting glucose
IC	Intermittent claudication
IGT	Impaired glucose tolerance
IIEF-5	the International Index of Erectile Function short form
LDL-C	Low-density lipoprotein cholesterol
LTPA	Leisure-time physical activity
MetS	Metabolic syndrome
NO	Nitric oxide
OGTT	Oral glucose tolerance test
OR	Odds ratio
PAD	Peripheral arterial disease
PP	Pulse pressure
RR	Relative risk
SBP	Systolic blood pressure
SCORE	Systematic Coronary Risk Evaluation
SD	Standard deviation
TASC II	The Trans-Atlantic Inter-Society Consensus
TC	Total cholesterol
TG	Triglycerides
WC	Waist circumference

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in text by their Roman numerals:

I. **Heikkilä A, Venermo M, Kautiainen H, Aarnio P, Korhonen P.** Physical activity improves borderline ankle-brachial index values in a cardiovascular risk population. Ann Vasc Surg. 2016 Apr; 32:50-6.

II. **Heikkilä A, Venermo M, Kautiainen H, Aarnio P, Korhonen P**. Short stature in men is associated with subclinical peripheral arterial disease. Vasa. 2016 Nov;45(6):486-490.

III. **Heikkilä A, Ettala OO, Kaipia A, Venermo M, Kautiainen H, Korhonen P.** Ankle-brachial index is worth measuring in men over 60 years old complaining erectile dysfunction. Submitted.

IV. **Heikkilä A, Kaipia A, Venermo M, Kautiainen H, Korhonen P.** The relationship of blood pressure and erectile dysfunction in men without previously diagnosed hypertension. J Sex Med. 2017 Nov;14(11):1336-1341.

1. INTRODUCTION

Peripheral arterial disease (PAD) affects approximately 202 million people around the world and associates with a high risk of myocardial infarction, stroke and death (Roger et al. 2011, Fowkes et al. 2013). The prevalence of PAD seems to be slightly greater in men than in woman, although there are differing results (Criqui & Aboyans 2015, Fowkes et al. 2013, Norgren et al. 2007). For every patient with symptomatic PAD there are another three to four individuals without typical symptoms, which makes it an underdiagnosed and undertreated disease (Fowkes et al. 1991, Hirsch et al. 2001).

A reliable, cheap and noninvasive method to detect PAD in a primary care setting is the measurement of the ankle-brachial index (ABI) (Dachun et al. 2010, Ankle Brachial Index Collaboration et al. 2008). ABI ≤ 0.90 is the most frequently used threshold for PAD. It has over 90% sensitivity and specificity to detect PAD, defined as >50% arterial stenosis in lower-extremity angiography (Carter 1968, Yao et al. 1969). The consistent relationship between low ABI and coronary artery disease (CAD) and cerebrovascular disease (CBVD) has been demonstrated in several studies(Hirsch et al. 2001, Ankle Brachial Index Collaboration et al. 2008). Even borderline ABI 0.91 – 1.00 has been shown to be associated with increased rates of major cardiovascular events and mortality compared with persons with normal ABI, i.e. 1.11 – 1.40 (Ankle Brachial Index Collaboration et al. 2008).

Older age, smoking and diabetes are the most important risk factors associated with PAD as well as declining ABI (Norgren et al. 2007, Kennedy et al. 2005, Allison et al. 2009). “Stop smoking and keep on walking” is a traditional precept for patient with intermittent claudication (IC). The relationship between physical activity and PAD has been established in a few heterogenous studies (Bertoni et al. 2009, Siscovick et al. 1997, Barone Gibbs et al. 2013). Physical activity has been associated with higher ABI values and may even reduce the incidence of asymptomatic PAD (Bertoni et al. 2009, Engstrom et al. 2001). Hypertension and higher low-density lipoprotein cholesterol (LDL-C) concentration are both associated with all forms of cardiovascular disease (CVD), including PAD (Norgren et al. 2007, Korhonen, Syvanen et al. 2009).

Adult height is determined mainly by genetic factors. Several studies have demonstrated a link between short stature and increased risk of CVD, especially CAD (Emerging Risk Factors Collaboration 2012, Paajanen et al. 2010, Rosenberg et al. 2014). In men, the association appears to be stronger than in women (Rosenberg et al. 2014). The relationship between height and PAD is unknown in the general population.

Erectile dysfunction (ED) is often considered as an early sign of CVD (C. Vlachopoulos et al. 2005, F. Montorsi et al. 2003, Ponholzer, Temml, Mock et al.

2005). ED shares the same risk factors as PAD, such as diabetes and hypertension (Doumas et al. 2006, Ponholzer et al. 2005). While an association between PAD and ED has been suggested, their unequivocal correlation remains to be demonstrated. It is therefore not clear whether men with ED should be considered for testing asymptomatic PAD (D. I. Feldman et al. 2016, Polonsky et al. 2009).

The present thesis was undertaken to investigate risk factors for PAD and increase the awareness of this underdiagnosed vascular disease in primary care. Special attention was paid to men who are known to suffer from CVD at a younger age than women (Benjamin et al. 2017).

2. REVIEW OF THE LITERATURE

2.1. Peripheral arterial disease

2.1.1. Pathophysiology

Peripheral arterial disease (PAD) is a narrowing of the arteries commonly supplying blood to the lower extremities. Other terms used for this disease are peripheral vascular disease, peripheral arterial occlusive disease, and lower extremity arterial disease. PAD is primarily the result of atherosclerosis. Since atherosclerosis is a systemic disease PAD is usually a sign of accumulation of fatty plaque also in other vascular beds, such as brain and heart. Other causes leading to narrowing of the lower extremity arteries may include injury, congenital abnormalities and irregular anatomy of muscles or ligaments. The plaque build-up in leg is illustrated in Figure 1.

Atherosclerosis is a chronic inflammatory syndrome where the artery wall is invaded by white blood cells, cholesterol, triglycerides, calcium and other remnants of dead cells combined with the proliferation of intimal-smooth-muscle cells creating an atheromatous plaque (Hansson & Hermansson 2011, Ross 1993). The plaque narrows the artery and reduces blood flow to the limb decreasing the oxygen and nutrients available to the tissue.

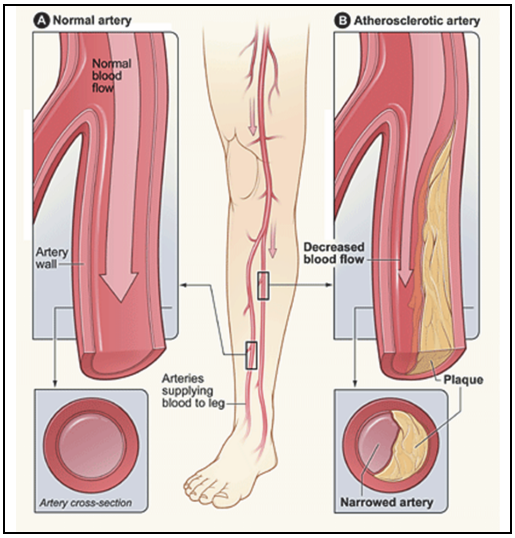

***Figure 1**. PAD affecting in the leg. Figure A shows a normal artery with normal blood flow. Figure B shows an artery with plaque blocking partially blood flow. Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services.*

2.1.2. Symptoms and signs

Symptoms of PAD can be deceptive, as a large number of individuals suffering from atypical lower limb discomfort or lack of all lower extremity symptoms, may still have limitations with walking (McDermott et al. 2001). Classically, an elderly patient with a history of cigarette smoking comes to a physician´s appointment complaining of pain, fatigue or discomfort in the calf muscles during exercise, a symptom known as intermittent claudication. This ischemic pain due to lactic acid and other anaerobic metabolites forces the patient to stop walking (Meru et al. 2006). The pain is relieved by rest within 10 minutes (Norgren et al. 2007). Atypical exertional leg pain can be defined as exertional leg symptoms that do not begin at rest, do not resolve within 10 minutes of rest and do not involve the calves (McDermott et al. 2002). The most severe degree of PAD is the critical limb ischemia (CLI) with gangrene, ulcer or rest pain in the lower limbs. The natural progression of PAD is not always straightforward judging by clinical manifestations. The majority of patients with CLI, have not suffered IC earlier (Matzke & Lepantalo 2001, Norgren et al. 2007). Therefore, the first sign of PAD can be an ulcer in a toe or a foot pain during the night, which eases by hanging the leg outside the bed.

A special focus must be placed on diabetic patients with neuropathy and elderly people with condition that limits mobility or otherwise leading a sedentary life. Therefore, the 2007 TASC II guidelines recommended that ABI should be routinely screened in all individuals 70 years or older, regardless of risk factors, and in all individuals between 50 and 69 years of age having a cardiovascular risk factor, particularly diabetes or smoking (Norgren et al. 2007).

2.1.3. Epidemiology

It is estimated that over 200 million people have PAD worldwide, symptoms varying from none to IC and CLI, which is the tip of the iceberg (Fowkes et al. 2013). The majority of the epidemiological studies come from highly developed countries and the most widely used method to detect PAD is the non-invasive measurement of the ankle-brachial index (ABI). A resting ABI of ≤ 0.90 is the most frequently used diagnostic threshold for PAD (Norgren et al. 2007, Aboyans et al. 2012). PAD is the third leading cause of cardiovascular mortality after coronary artery disease (CAD) and stroke (Fowkes et al. 2013).

Several epidemiological studies have reported a broad spectrum of overall prevalence of asymptomatic PAD. The numbers naturally depend on the definition of PAD and the study population. The prevalence rates vary between 3% and 18% to as high as 29%, increasing with the age of the population (Selvin & Erlinger 2004, McDermott et al. 2005, Diehm et al. 2004, Hirsch et al. 2001). The prevalence seems to be higher among men than women for more severe and symptomatic disease (Criqui & Aboyans 2015). In the literature the estimates of

PAD incidence are frequently based on symptomatic study populations (Ingolfsson et al. 1994, Bowlin et al. 1994). Data on asymptomatic PAD incidence based on ABI are scarce. In the Limburg Peripheral Arterial Occlusive Disease Study, PAD was defined by ABI < 0.95 and after a 7.2-year follow-up the overall incidence for asymptomatic PAD was 9.9 per 1000 person-years at risk (7.8 for men and 12.4 for women) (Hooi et al. 2001). For symptomatic PAD, the incidence rates were 1.0, 0.4 and 1.8 respectively (Hooi et al. 2001).

In 2001 the PARTNERS (PAD Awareness, Risk, and Treatment: New Resources for Survival) study reported the ABI values of 6979 screened subjects from 350 primary care practices (Hirsch et al. 2001). PAD was defined as an ABI of ≤ 0.90 or a prior history of lower extremity revascularization. Participants aged ≥ 70 or aged 50–69 years with history of cigarette smoking or diabetes were evaluated. PAD was detected in 29% of the total population, only 11% of them having classical claudication symptoms, thus demonstrating the asymptomatic nature of PAD (Hirsch et al. 2001).

In 2013, Fowkes et al published a systematic review of the global estimates of prevalence for PAD (Fowkes et al. 2013). Twenty-two studies from high-income countries and 12 from low- and middle-income countries were included with 112 027 participants (Fowkes et al. 2013). PAD was defined by ABI ≤ 0.90. At the age of 45-49 years the prevalence of PAD in high-income countries was 5% in both genders and at the age of 85-89 years the rates increased to 18% and 19% in women and men, respectively (Fowkes et al. 2013). Among men, the prevalence of PAD in all age groups was lower in low- and middle-income countries compared to high-income countries. Among women the difference was similar, except for younger women it was the opposite (Fowkes et al. 2013). Worldwide, the number of people with peripheral artery disease has increased by almost 25% between 2000 and 2010 (Fowkes et al. 2013).

The prevalence of IC varies between 1% to 7% in the general population (Diehm et al. 2004, Meijer et al. 1998, Sigvant et al. 2007, Fowkes et al. 1991, Norgren et al. 2007). The rates seem to increase with age and are influenced by the study design and definitions. The annual incidence and prevalence of CLI were 0.35% and 1.33%, respectively, in a large database study based on insurance claims from the US including 12 million adults aged over 40 years (Nehler et al. 2014). Earlier TASC II estimated the incidence of CLI to be 500 to 1000 new patients every year per 1 million people in western world (Norgren et al. 2007).

In summary, it is clear that PAD is an underdiagnosed disease, with the majority of patients being asymptomatic (Hirsch et al. 2001, Fowkes et al. 1991, Diehm et al. 2004). It is also probable that we will see a growth in the prevalence of PAD in the future, especially in low- and middle-income countries (Criqui & Aboyans 2015, Fowkes et al. 2013).

2.1.4. Diagnosis

The primary clinical assessment of PAD is a patient history and physical examination. A history of IC should raise a suspicion of PAD but underestimates the real prevalence of PAD (Criqui et al. 1985). Atherosclerosis being a systemic disease, patients with PAD usually have multiple cardiovascular risk factors and other comorbid cardiovascular diseases, which guides the physician´s decision-making.

The circulatory system should be evaluated as a whole, including measurement of blood pressure and auscultation of the heart (Norgren et al. 2007). Screening for abdominal aneurysms should be consider, thus the prevalence of abdominal aneurysms is 5% among PAD patients (Li et al. 2013). Inspection of the feet can give hints from diminished arterial flow, for example decreased hair growth, changes in color or temperature and muscle atrophy. Ulcers and gangrene can be seen in patients with CLI. More specific peripheral vascular examination requires palpation of the radial, ulnar, brachial, carotid, femoral, popliteal, dorsalis pedis and posterior tibial pulses, focusing on the lower extremities. Palpable pedal pulses on examination have a negative predictive value of over 90% and may rule out PAD in many patients (Norgren et al. 2007, Londero et al. 2016). However, the accuracy of the pulse palpation is limited. In a recent study by Londero et al, 18 681 men were screened for PAD with bilateral pulse palpation and ABI measurement (Londero et al. 2016). They concluded that pulse palpation is an effective method for excluding PAD but only if all four pedal pulses are present (Londero et al. 2016). If clear pedal pulses are not palpable, ABI should be measured. The validity of pulse palpation has been argued in several studies and it seems that the finding of absent pedal pulses tends to over-diagnose PAD (Collins et al. 2006, Stoffers et al. 1997, Criqui et al. 1985). Furthermore, in a study of 403 primary care subjects, the sensitivity of pulse palpation to detect PAD was as low as 18% in the early stages of PAD (Collins et al. 2006). Thus, the diagnosis of PAD must be confirmed with non-invasive testing using the ABI, or other hemodynamic or imaging procedures (Norgren et al. 2007).

Ankle-brachial index

As one of the most available, non-invasive and cheapest screening tests for PAD, the ABI is a highly convenient measurement in primary care. The ABI, also known by the ankle-arm index, the ankle-brachial blood pressure index and the ankle-arm ratio, is an appropriate measurement for CVD risk assessment in a community setting. The PARTNERS study identified several obstacles to the broader use of ABI in primary care, such as staff training and availability, time constraints and reimbursement (Hirsch et al. 2001). To overcome these issues by providing guidance and a standardized method to determine the ABI, The American Heart

Association published a scientific statement for measurement and interpretation of the ABI in 2012 (Aboyans et al. 2012). A biomarker that has both a diagnostic and a prognostic role is a special advantage that makes the ABI the most feasible vascular marker in the setting of primary care.

Before the ABI measurement, the patient should be at rest for 5 to 10 minutes in the supine position, head and heels supported, in a room with a comfortable temperature (Aboyans et al. 2012). Smoking before the measurement decreases the ABI, therefore a smoking abstinence of 2 hours before the measurement is recommended (Yataco & Gardner 1999). The cuff should be chosen appropriately according to the limb size but the width should be at least 40% of the limb circumference (Aboyans et al. 2012). Moreover, the cuff should be placed 2 centimeters above the medial malleolus. Doppler ultrasound probe is used to detect the arterial pulse from the posterior tibial artery (ATP) and dorsalis pedis artery (ADP) in both legs. After this, the cuff is inflated progressively up to 20 mmHg above the level of Doppler signal disappearance and then deflated slowly until the signal reappears. This indicates systolic blood pressure (SBP) in the artery. The detection of the brachial blood flow should also be done by Doppler when measuring SBP in each arm (Aboyans et al. 2012). The use of the cuff should be avoided in the case of a distal lower limb bypass for risk of thrombosis (Aboyans et al. 2012). The measurement of ABI is illustrated in Figure 2.

Mathematically the ABI is calculated by dividing the SBP at the ankle by the SBP in the arm. The higher SBP of the right or the left arm is used (Aboyans et al. 2012). However, there are different modes of calculating ABI depending on which SBP is used in the legs, ADP or ATP. The mode of calculation of the ABI has a notable effect on the estimation of PAD prevalence and associations with CVD risk factors within a population (Espinola-Klein et al. 2008, Lange et al. 2007, Aboyans et al. 2002). In the Multi-Ethnic Study of Atherosclerosis with 6590 subjects, the authors calculated ABI in three ways from both legs: with the lowest ankle pressure (ADP/ATP), with the highest ankle pressure and with the mean of the ankle pressures (Allison et al. 2010). The index ABI used was the lower of the ABIs calculated from the left and right legs (Allison et al. 2010). The prevalence of PAD was 3.95 times higher in women and 2.74 times higher in men comparing the lowest to the highest ankle pressure (Allison et al. 2010). In addition, Espinola-Klein et al suggested that more patients at high risk of CV events could be identified if the lower ankle pressure was used (Espinola-Klein et al. 2008). According to the AHA guidelines, when ABI is used as a diagnostic tool to evaluate patients with symptoms of PAD, both legs should be reported separately and the higher of the two ankle pressures should be used, because it better describes the perfusion of the leg (Aboyans et al. 2012). However, the same guideline states that, when ABI is used as a prognostic marker of CVD events and mortality, the lower of the ABIs of the left and right leg should be used (Aboyans et al. 2012).

Several studies have assessed the intra-observer and inter-observer reproducibility of ABI with overall data demonstrating that ABI is a valid and appropriate way to detect PAD (Fowkes et al. 1988, Holland-Letz et al. 2007, Endres et al. 2006, Benchimol et al. 2009, de Graaff et al. 2001). Two studies evaluated the reliability of ABI measurement by different medical training backgrounds; vascular physician, family physician and trained nurse/assistant, and found no differences among observers (Holland-Letz et al. 2007, Endres et al. 2006) . However, to keep single measurement error to a minimum, it is recommended that repeated measurements are done if the initial ABI is close to the threshold value of 0.9 (between 0.8 and 1.0) (Aboyans et al. 2012). A single ABI value < 0.8 has a 95% positive predictive value for the diagnosis of PAD; and a single ABI > 1.0 has a 99% negative predictive value for PAD (Stoffers et al. 1996).

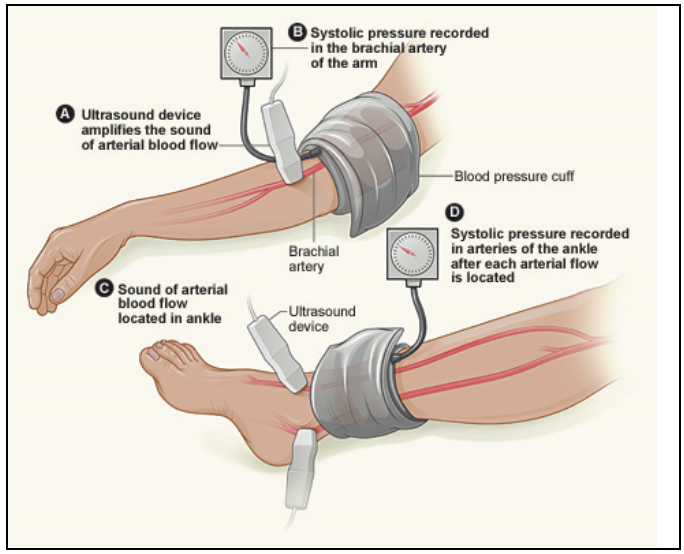

Figure 2. *The measurement of ankle-brachial index. Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services.*

A resting ABI of ≤ 0.90, measured with the Doppler technique, is the most commonly used cut-off value for PAD (Norgren et al. 2007, Aboyans et al. 2012). Several studies have evaluated the diagnostic performance of this threshold to detect >50% stenosis identified by different imaging methods, including color duplex ultrasound (Allen et al. 1996, Premalatha et al. 2002, Schroder et al. 2006, Williams et al. 2005) and angiography (Lijmer et al. 1996, Niazi et al. 2006, Guo et al. 2008). All these studies reported quite high specificity (83%-99%) but lower sensitivity (69%-79%). Lower sensitivities were found among diabetic patients (Premalatha et al. 2002, Williams et al. 2005). In addition, two of these studies concluded that ABI calculated from the lower SBP of the two ankle arteries (ADP

and ATP) identified PAD more accurately and had better sensitivity than ABI calculated from the higher ankle artery SBP (Niazi et al. 2006, Schroder et al. 2006). According to the AHA statement, ABI values from 0.91 to 1.0 should be considered as borderline and the overall cardiovascular risk history should be considered when interpreting the ABI results (Aboyans et al. 2012).

The greatest limitation of ABI is falsely high values in patients with mediasclerosis. In some patients with medial calcinosis, diabetes or renal insufficiency, tibial arteries at the ankle become non-compressible due to mediasclerosis (Goss et al. 1989, Leskinen et al. 2002). This leads to a false elevation of the ankle pressure and abnormally high ABI values >1.40. When mediasclerosis is present, PAD cannot be detected by ABI which complicates the clinical decision-making and PAD diagnosis (Suominen et al. 2008). In these cases, other non-invasive diagnostic tests should be performed for a reliable diagnosis of PAD. As mediasclerosis does not affect digital arteries, toe pressures and the toe-brachial index are the first choices to evaluate perfusion in these patients (Sahli et al. 2004, Aboyans et al. 2012). Transcutaneous oxygen tension measurements and vascular imaging have also been used. However, these tests are not suitable for primary care setting.

Occasionally, a patient may have typical IC symptoms with normal resting ABI and pedal pulse findings. This can be seen in patients who have less severe stenosis or isolated proximal stenosis (R. Stein et al. 2006, Norgren et al. 2007). During exercise, the increased inflow velocity will make these lesions hemodynamically significant causing symptoms of IC. In these cases, post-exercise ABI performed by walking on a treadmill, is an excellent instrument in differential diagnosis. First the resting ABI is measured and then the patient is asked to walk (typically on a treadmill at 3.2 km/h, 10%–12% grade) until claudication pain occurs or a maximum of 5 minutes. After this the ABI measurement is repeated. A decrease in ABI of > 20% is diagnostic for PAD (Aboyans et al. 2012).

The options for imaging the vascular tree of the limb include digital subtraction angiography, magnetic resonance angiography, computed tomographic angiography and duplex ultrasound. As a diagnostic method, digital subtraction angiography has been replaced mostly by less invasive methods in vascular imaging. The decision for imaging is made by a vascular surgeon with a sentiment of revascularization if an appropriate lesion is detected. With CLI patients the decision is usually easy but among patients suffering from IC or atypical leg symptoms, each patient must be considered individually, not only by the distance of the claudication but also by the impact on quality of life and ability to work. In primary care, a general practitioner takes part in the decision-making when evaluating and differential-diagnosing these patients with the instruments available, before referring them to a vascular specialist.

2.1.5. Risk factors

Cigarette smoking, diabetes and aging are the strongest risk factors for PAD (Norgren et al. 2007). The risk factors are similar, but not identical, to those for other cardiovascular diseases, such as CAD (Hirsch et al. 2006, Fowkes et al. 1992, Criqui 2001). In the Health Professionals Follow-up Study, smoking, type 2 diabetes, hypertension, and hypercholesterolemia accounted for 75% of risk associated with development of clinically significant PAD among men (Joosten et al. 2012). Figure 3 illustrates the meta-analyses of the effect size of 11 risk factors, data compiled by Fowkes et al (Fowkes et al. 2013). The prevalence and incidence of PAD are both clearly age-related, rising to >10% among patients in their 60s and 70s (Criqui & Aboyans 2015).

It must bear in mind that many studies of PAD risk factors are based on cross-sectional associations, as longitudinal studies are time-consuming and expensive to carry out. The reported results from these cross-sectional studies cannot definitively prove causation because it is not known whether the risk factor precedes the disease or vice versa.

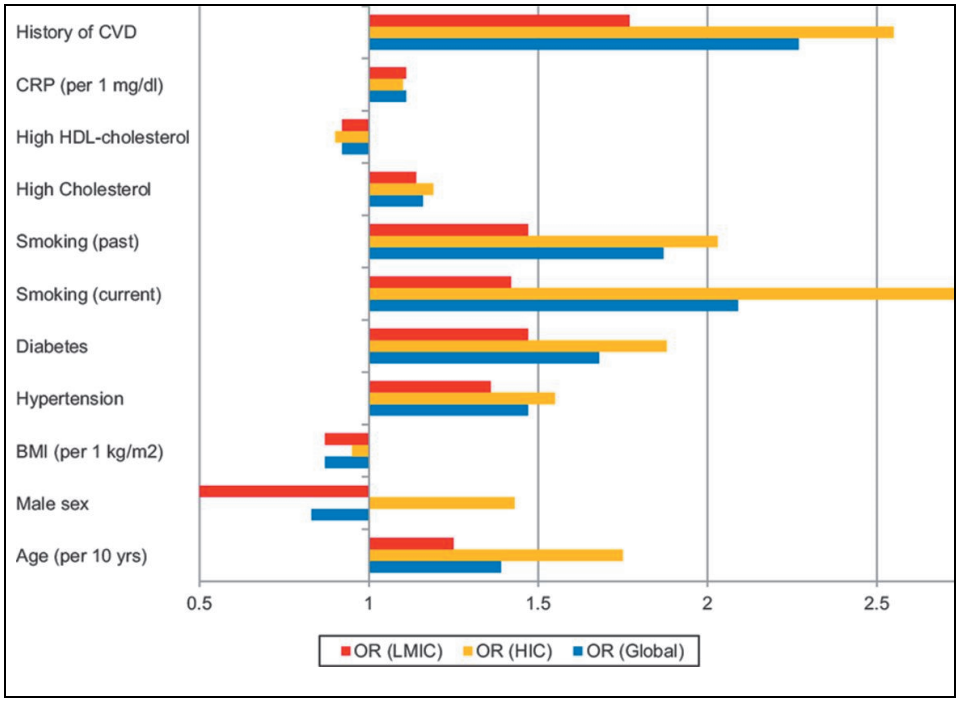

***Figure 3**. Odds ratios for peripheral artery disease in high-income countries (HIC) and low- and middle-income countries (LMIC). BMI, body mass index; CVD, cardiovascular disease; CRP, C-reactive protein; HDL, high-density lipoprotein; LMIC, low-and middle-income countries; HIC, high income-countries. Reprinted with permission from Wolter Kluwers. Criqui et al. Circ Res. 2015 Apr 24;116(9):1509-26 and based on data from Fowkes FG et al. Lancet. 2013 Oct 19;382(9901):1329-40.*

Smoking

Cigarette smoking is an exceptionally strong etiologic risk factor for PAD (Criqui et al. 1997). It seems to play a more prominent role in PAD than in other CVDs. This relationship was established for the first time in 1911, when a German neurologist Wilhelm Heinrich Erb reported that IC was three-times more common in smokers compared to non-smokers (Erb 1911). Fowkes et al reported from the Edinburgh Artery Study that current smokers are almost four times as likely to develop asymptomatic PAD than non-smokers (Fowkes et al. 1991). Two decades later the same authors found consistent results between smoking and PAD (defined by ABI ≤ 0.90), with meta-OR for current smoking of 2.72 in high-income countries and 1.42 in low- and middle-income countries in a large systematic review (Fowkes et al. 2013). According to several prospective and cross-sectional studies, smoking increases the risk of IC (Reunanen et al. 1982, Hooi et al. 2001, Leng et al. 1995, Fowkes et al. 1992), expedites the PAD diagnosis (Norgren et al. 2007) and has a clear dose-response relationship, with relative risk for symptomatic PAD 1.9 for moderate smokers and 3.9 for heavy smokers (Willigendael et al. 2004, Joosten et al. 2012). In addition, more than 80% of the patients with symptomatic PAD are current or former smokers (G. D. Smith et al. 1990, Meijer et al. 1998). On the other hand, smoking cessation is associated with a decline in the incidence of IC (Ingolfsson et al. 1994, Fowkes et al. 1991) as well as mortality (Faulkner et al. 1983, Jonason & Bergstrom 1987). However, even after 20 years of smoking cessation the association between smoking and increased risk of incident clinical PAD was reported by the Health Professionals Follow-up Study (Joosten et al. 2012). Only few studies have reported on the association between passive smoking and PAD. In a recent Scottish study, secondhand smoke exposure (≥ 40 h per week) was associated with significantly increased risk of PAD among 5,686 never smokers (Lu et al. 2013). Similar results were reported by He et al among Chinese women who had never smoked (Y. He et al. 2008).

Diabetes

It is estimated that over half a million people have diabetes in Finland and 422 million worldwide (Diabetes: Current Care Guidelines Abstract 2018, WHO Global Report on Diabetes 2016). The association between diabetes and PAD is well-established, with odds ratios ranging from 1.9 to 4.1 (Meijer et al. 2000, Newman et al. 1993, Murabito et al. 1997, Allison et al. 2006) and the association seems to be significantly higher in high-income countries than in low- and middle-income countries (Fowkes et al. 2013). In symptomatic patients, IC is about two-fold more common among diabetics than among non-diabetics (Norgren et al. 2007). In detail, the risk of PAD is increased by 26% for every 1% increase in hemoglobin A1c (Selvin et al. 2004). PAD also appears more aggressive among diabetics and the severity and duration of diabetes increases the risk of developing

PAD (Norgren et al. 2007, Beks et al. 1995, Katsilambros et al. 1996). Moreover, the risk of developing CLI is higher in diabetics than in nondiabetics (McDaniel & Cronenwett 1989, Bowers et al. 1993). A diabetic PAD patient has a 5- to 15-fold greater probability to undergoing a major amputation than a nondiabetic one (Jude et al. 2001, Most & Sinnock 1983). In Finnish population, every other lower limb amputation was performed on a diabetic patient in the year 2000 (Eskelinen et al. 2004).

Dyslipidemia

Total cholesterol (TC) as a potential risk factor for PAD has been widely examined. A significant association has been demonstrated between these two in several studies (Newman et al. 1993, Murabito et al. 1997, Meijer et al. 2000), with occasional null finding after adjustment for other lipid measures (Ness et al. 2000). A protective effect of high-density lipoprotein cholesterol (HDL-C) is another typical find in most studies (Curb et al. 1996, Ness et al. 2000, Meijer et al. 2000, Murabito et al. 2002). But the relationship between PAD and triglycerides is debatable. In both of two studies, the Edinburgh Artery study and the Framingham Offspring study, triglycerides were significant in univariate analysis but dropped out in multivariate models (Newman et al. 1993, Fowkes et al. 1992). On the other hand, there are studies where the association holds even in multivariate analysis (Bainton et al. 1994, Katsilambros et al. 1996).

Although there is consistent evidence from numerous clinical and genetic studies that low-density lipoprotein cholesterol (LDL-C) causes atherosclerotic cardiovascular disease (Ference et al. 2017), the results regarding the association between PAD and LDL-C are not consistent (Fowkes et al. 2013, Ness et al. 2000). However, current recommendations for the management of dyslipidemia in PAD patients with statins are based on treatment goals of LDL-C levels (Norgren et al. 2007, Rooke et al. 2011). The evidence supporting the use of statins to lower LDL-C levels in PAD comes from the Heart Protection Study that included 6748 participants with symptomatic PAD (Heart Protection Study Collaborative Group 2002). Among these patients (even in the absence of a prior myocardial infarction or stroke), at 5-year follow-up, aggressive LDL-C lowering with simvastatin, was associated with a significant reduction in cardiovascular events (19% relative reduction and 6.3% absolute reduction) (Heart Protection Study Collaborative Group 2002).

Recently, the ratio of TC and HDL-C has been proposed for a possible model for PAD risk factor analysis (Natarajan et al. 2003, Criqui et al. 2005). Ridker et al reported from the Physician´s Health Follow-up Study that the TC to HDL-C ratio was the strongest independent lipid predictor of development of symptomatic

PAD, with patients in the highest quartile having almost four times the risk of IC compared with those in the lowest quartile (Ridker et al. 2001).

Hypertension

Approximately two million Finnish adults suffer from high blood pressure (Hypertension: Current Care Guidelines Abstract 2014). Worldwide, every fourth adult has hypertension and the number is growing (Kearney et al. 2005). The high prevalence of hypertension makes it a significant contributor to the total burden of PAD in the population. Several large population-based studies have reported independent associations of hypertension or SBP and PAD, with odds ratios varying from 1.50 to 2.2 (Murabito et al. 1997, Murabito et al. 2002, Newman et al. 1993, Allison et al. 2006). Interestingly, in the Cardiovascular Health Study DBP was not significantly associated with PAD, with similar results reported from the Rotterdam Study (Meijer et al. 2000, Newman et al. 1993). A large prospective cohort study of men by Joosten et al evaluated the four most important risk factors for PAD - smoking, hypertension, hypercholesterolemia and diabetes - with findings that highlighted the importance of hypertension as a major risk factor for PAD, with a population attributable risk of more than 40% (Joosten et al. 2012). Only current smoking was a more contributive risk factor for PAD. Earlier, Murabito et al reported an almost as high population attributable risk of 30% for hypertension and IC in both genders (Murabito et al. 1997).

Physical activity

Several cross-sectional studies have recognized the relation between physical activity and ABI values. A robust cross-sectional study from the United States, with over three million self-referred participants demonstrated that subjects who reported any physical activity had significantly lower odds of PAD (OR 0.64) (R. A. Stein et al. 2015). Higher frequency of physical activity was also associated with lower prevalence of PAD in a graded manner (R. A. Stein et al. 2015). The associations were significant even after adjustment for multiple cardiovascular risk factors (R. A. Stein et al. 2015). In addition, subjects with intermittent claudication, angina, and lower extremity neuropathy, were excluded from the analyses (R. A. Stein et al. 2015). Siscovik et al reported from the Cardiovascular Heart Study an inverse relation between exercise intensity and the prevalence of a low ABI (<0.9) in subjects over 65 years of age (Siscovick et al. 1997). In the Multi-Ethnic Study of Atherosclerosis, moderate-to-vigorous and intentional exercise associated with higher ABI value (Bertoni et al. 2009). As discussed earlier, care should be taken in reviewing the results of cross-sectional studies. For example, low physical activity might cause IC, but IC might just as plausibly cause low physical activity. A prospective study by Delaney et al involved 5,656 CVD-

free individuals, with a mean age of 61 years, and of whom 53% were female, derived from the Multi-Ethnic Study of Atherosclerosis (Delaney et al. 2013). The authors suggested that participation in intentional exercise prevents incident PAD (ABI ≤ 0.9) with the risk ratio (RR) of 0.85 (Delaney et al. 2013). Other follow-up studies with more comorbid cohorts have demonstrated that physical activity associates with higher ABI values (Barone Gibbs et al. 2013, Engstrom et al. 2001), and may even reduce the incidence of asymptomatic PAD (Hooi et al. 2001). A recent randomized trial using a six-month supervised exercise program reported a significant improvement in ABI among subjects with uncomplicated type 2 diabetes and ABI <1.00 (Barone Gibbs et al. 2013).

Obesity

The relationship between obesity and PAD is not as clear as one would think. The association is more controversial than with other CVDs. There are a large number of population-based studies that have failed to find a significant association between obesity and PAD or IC (Hooi et al. 2001, Murabito et al. 2002, Meijer et al. 2000, Allison et al. 2006). Newman et al even reported from The Cardiovascular Health Study that higher body mass index (BMI) protected significantly against PAD (Newman et al. 1993). A study from Taiwan concurred with these results among 610 patients with type 2 diabetes (Tseng 2003). As obesity is implicated in the etiology of other risk factors for PAD, such as diabetes, dyslipidemia and hypertension, it is possible that the association between obesity and PAD is overlooked in multivariate models. In addition, chronic ailments in the elderly, including PAD, may lead to weight loss and therefore corrupt the correlation between obesity and PAD.

Gender

The association between gender and PAD seems to be related to the severity of the disease to some degree (Criqui & Aboyans 2015). Sex differences in the incidence and prevalence of other CVDs are more distinct. In the Framingham Study, the annual incidence of IC for all ages combined was 7.1 per 1000 in men and 3.6 per 1000 in women, for a male to female ratio of 2.0 (Kannel & McGee 1985). The prevalence ratios for IC in the Rotterdam Study and in the Framingham Offspring Study were 1.8 and 2.4, respectively (Meijer et al. 1998, Murabito et al. 2002). When PAD is diagnosed on the basis of ABI measurement these ratios seem to decline and are even inverse. For example, in the Rotterdam Study, the prevalence of ABI-based PAD was lower in men than in women, with a ratio of 0.8 (Meijer et al. 1998). A population-based study from Gallotta et al reported prevalence of PAD, defined as ABI <0.9, to be similar in both genders, with male to female ratios by age of 0.89 to 0.99 (Gallotta et al. 1997). McDermott et al reported from the

Multi-Ethnic Study of Atherosclerosis that PAD prevalence (ABI <0.90) was equal in men and women (3.7%), but borderline values of ABI (0.90–0.99) were much higher in women (10% versus 4%) (McDermott et al. 2005). From the same study population, a subset of participants with normal ABI values (1.00 to 1.30), and with no major PAD risk factors (smoking, diabetes, dyslipidemia, hypertension) was analyzed and ABI was reported to be 0.02 lower in women than in men (Aboyans et al. 2007). Apparently, women may have lower normal distribution of the ABI than men. This possibility was acknowledged also by Fowkes et al when they recently reported higher prevalence rates of PAD in women than in men in low- and middle-income countries (Fowkes et al. 2013).

Body height

There are a limited number of studies reporting on the effect of body height on PAD or ABI. A report from the Edinburgh Artery Study suggested that height may explain a portion of the difference in ABI values between men and women, an observation discussed earlier (Fowkes et al. 1991). In a low-risk subset of the study population derived from the San Luis Valley Diabetes Study, a significant but moderate association between body height and ankle pressure was reported (Hiatt et al. 1995). The results were adjusted for arm pressure, sex, diabetes status and age. For each 10cm in height, there was an approximate 1 mmHg increase in ankle pressure (Hiatt et al. 1995). The mechanism for this association might be more complex than the progressive SBP increase with greater distance from the heart. In a smaller study population without previous clinical CVD, a positive correlation between ABI and body height was also observed in both genders (London et al. 1995). However, in the Multi-Ethnic Study of Atherosclerosis this relationship turned out to be only marginal, ABI being only 0.003 higher for every 10cm height increase, after adjusting for sex, ethnicity and risk factors (Aboyans et al. 2007).

Chronic renal insufficiency

There is a consistent association between chronic renal insufficiency and PAD, particularly in the more severe stage of renal disease requiring dialysis (Wattanakit, Folsom, Selvin et al. 2007, A. O'Hare & Johansen 2001, A. M. O'Hare et al. 2004, Liew et al. 2008). Most studies concentrating on this association include patients with symptomatic PAD and usually with critical limb ischemia. A recent study from France demonstrated that chronic kidney disease is an independent predictor of one-year mortality among 1,010 patients hospitalized for PAD (Lacroix et al. 2013). Earlier Pasqualini et al had made the same prediction concerning long-term mortality with symptomatic PAD patients (Pasqualini et al. 2007). From the Atherosclerosis Risk in Communities Study, an increase in risk for incident PAD, defined as ABI <0.9, IC or PAD-related hospital discharge, was

observed in subjects with chronic kidney disease, with a multivariable adjusted RR of 1.56 (Wattanakit et al. 2007).

2.1.6. Co-existing atherosclerotic disease

Given the similar risk factors and the systemic nature of atherosclerosis, PAD and other cardiovascular and cerebrovascular diseases commonly occur together (Norgren et al. 2007). Figure 4 illustrates this typical overlapping. The TASC II working group stated that half of the patients diagnosed with PAD, also have CAD and CBVD in a primary care setting and because of this only 20% to 30% of patients with PAD die from non-cardiovascular causes (Norgren et al. 2007).

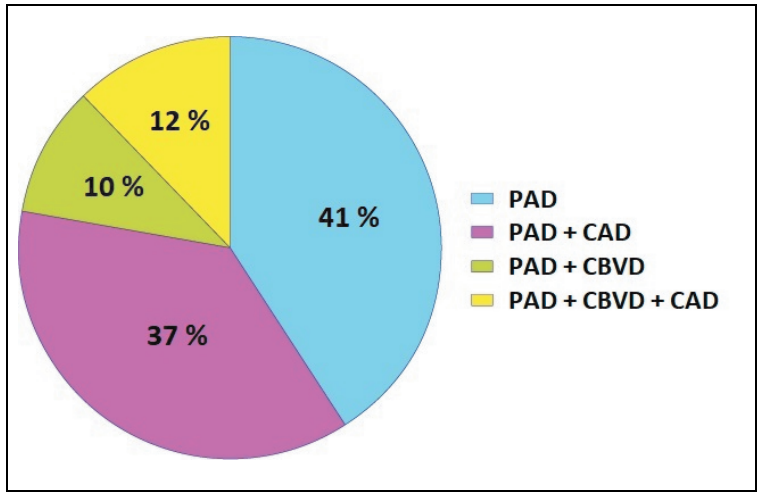

Figure 4. *The prevalence and overlapping of common manifestations of atherosclerosis. PAD indicates peripheral arterial disease; CBVD, cerebrovascular disease; and CAD, carotid artery disease. Modified from Finnish current care guideline for peripheral arterial disease (2010) and based on data from (Bhatt et al. 2006, Aronow & Ahn 1994, CAPRIE Steering Committee 1996).*

Coronary artery disease

Subjects with PAD, defined as ABI<0.9, had 2.5 times as high prevalence of history of myocardial infarction than those without PAD, in the Cardiovascular Heart Study (Newman et al. 1993). Vice versa, the patients with a history of myocardial infarction had 2.1 times higher prevalence of PAD versus those without (Newman et al. 1993). Murabito et al reported from the Framingham Offspring Study, with a predominantly middle-aged sample, that the prevalence of CAD increased with decreasing ABI values, and CAD was associated with a more than two-fold increase in the odds of PAD (Murabito et al. 2002). Moreover,

autopsy studies have demonstrated twice as much significant stenosis in the iliac and carotid arteries of patients dying from myocardial infarction than from other causes (Norgren et al. 2007).

Cerebrovascular disease

The global Reduction of Atherothrombosis for Continued Health registry has demonstrated a high prevalence of concomitant CAD and CBVD among PAD patients (Bhatt et al. 2006). In this survey over 60% of patients with PAD had clinical evidence of atherosclerotic disease in other vascular beds. In 2010, the Finnish current guideline for peripheral arterial disease (Peripheral arterial disease: Current Care Guidelines Abstract 2010) combined the results of the previous survey and two other studies (Bhatt et al. 2006, Aronow & Ahn 1994, CAPRIE Steering Committee 1996). According to the guideline, 10% of PAD patients also suffer from CBVD, and 12% have both CBVD and CAD (Figure 4) (Peripheral arterial disease: Current Care Guidelines Abstract 2010). The relationship between PAD and CBVD is not as strong with PAD and CAD. A meta-analysis conducted by Fan et al suggested that low ABI (ABI< 0.9) appears to be an independent predictor for ischemic and recurrent stroke events, with RR of 1.83 and 3.02, respectively (Fan et al. 2013). In a more recent meta-analysis of 11 studies (three of those included in Fan et al meta-analysis (Fan et al. 2013)) the association between low ABI and recurrent stroke was affirmed (Hong et al. 2016). Surprisingly in the Atherosclerosis Risk in Communities study, there was no association of ABI ≤ 0.9 with stroke or transient ischemic attack in women despite a strong association reported in men (Zheng et al. 1997).

2.1.7. PAD and ABI as predictors of mortality and morbidity

PAD is associated strongly and independently with an increased risk of incident CVD morbidity and mortality. Thus, the presence of PAD may serve as a prognostic marker for underlying atherosclerotic progressions in other vascular territories. The Whitehall Study was one of the first to demonstrate IC as a significant predictor of CVD mortality, even after adjusting for CVD risk factors and excluding subjects with baseline cardiac ischemic disease (G. D. Smith et al. 1990). The development of noninvasive measures such as the ABI enabled further research of the association between PAD and CVD. After this, many prospective studies corroborated the association between ABI and CVD morbidity and mortality (Kornitzer et al. 1995, Newman et al. 1993, Newman et al. 1999, Vogt et al. 1993). Criqui and Aboyans recently gathered a comprehensive summary of studies on the association of PAD with various mortality and morbidity outcomes, limited to studies using noninvasive measures, mostly ABI with the cut point of 0.90 (Criqui & Aboyans 2015). Adjustment with conventional risk factors was

carried out in all the studies. For total mortality, CVD mortality and CVD morbidity, the hazard ratios were in the range of 1.1-3.4, 1.3-6.3, 1.7-2.1, respectively (Criqui & Aboyans 2015).

In 2008, a robust meta-analysis of 48,294 individuals from 16 cohorts, with a mean age ranging from 47 to 78 years, demonstrated a reverse-J-shaped association between ABI and mortality (Figure 5) (Ankle Brachial Index Collaboration et al. 2008). In both genders, low ABI (≤0.9) carried an approximately three-fold risk of all-cause death compared with a normal ABI (1.11–1.40), and a similar pattern was observed for cardiovascular mortality (Ankle Brachial Index Collaboration et al. 2008). Fowkes and colleagues evaluated the ABI also as a continuous variable and even subjects with borderline ABI values of 0.91-1.00 had increased rates of mortality compared to the lowest risk subjects with ABI of 1.11 to 1.40 (Ankle Brachial Index Collaboration et al. 2008). For an ABI >1.40 the hazard ratios were also increased, 1.38 for men and 1.23 for women (Ankle Brachial Index Collaboration et al. 2008).

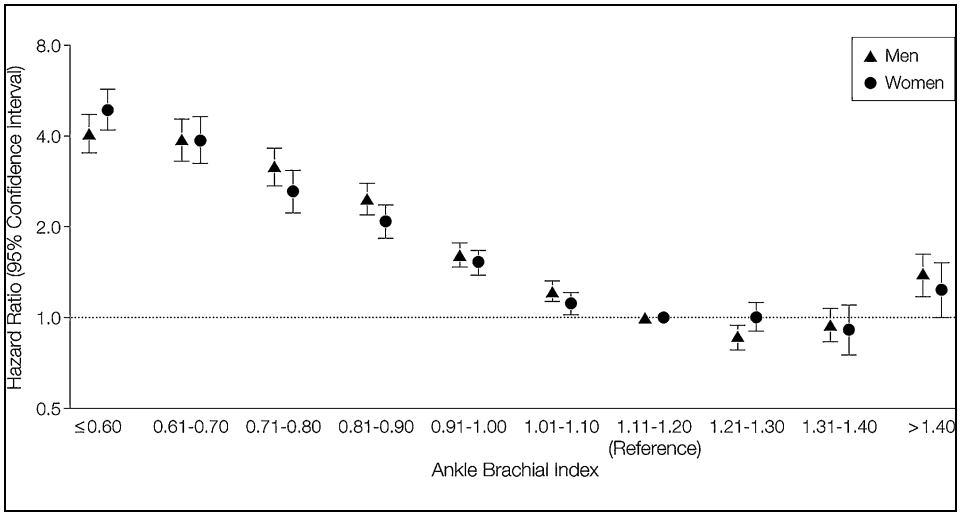

Figure 5. *Hazard ratios for total mortality in men and women by ABI at baseline for all studies combined in the ABI Collaboration. Hazard ratios are not adjusted for age or cardiovascular risk factors. Reproduced with permission from Ankle Brachial Index Collaboration. JAMA. 2008 Jul 9;300(2):197-208. Copyright © (2008) American Medical Association. All rights reserved.*

Indicative of vascular calcification, abnormally high ABI >1.4 is commonly seen in patients with diabetes or renal insufficiency (Goss et al. 1989, Leskinen et al. 2002). In these patients, high ABI values might be falsely higher, thus, masking the underlying PAD (Aboyans et al. 2008). Allison et al reported from the PARTNERS study that high ABI (≥1.4) correlated with stroke and congestive heart failure but not with myocardial infarction and angina (Allison et al. 2008). A paper from the Multi-Ethnic Study of Atherosclerosis highlighted a U-shaped

association between ABI and mortality risk (Resnick et al. 2004). In detail, both high (ABI >1.4) and low (ABI <0.9) ABI were correlated positively with higher risk for both all-cause mortality and CVD mortality than normal ABI (Resnick et al. 2004). O´Hare and colleagues came to the same conclusion with 5748 participants derived from the Cardiovascular Heart Study with an observation that the association of a high ABI with mortality was stronger in men than in women and in younger than in older participants (A. M. O'Hare et al. 2006). There are also reports with inconsistent results. For example, from the Atherosclerosis Risk in Communities study with 14 777 participants Wattanakit et al reported that age, sex, and race-adjusted CVD event rates per 1000 person-years were 8.1 in the normal ABI group and 7.6 in the ABI>1.4 group (Wattanakit, Folsom, Duprez et al. 2007).

The fate of the PAD patient´s leg has improved over the years. From 2000 to 2008 in the US, the overall rate of lower extremity amputation decreased significantly among PAD patients, from 7258 to 5790 per 100 000 (Jones et al. 2012). A probable explanation for this could be the increased use of endovascular and surgical revascularization after the year 2000, combined with the improved screening and detection of PAD and patients at risk for lower-extremity amputations (Norgren et al. 2007, Luther et al. 2000, Goodney et al. 2009). The prognosis for PAD patient undergoing a major lower-extremity amputation is still poor, with almost half of all patients dying within a year of amputation (Jones et al. 2013).

2.2. Erectile Dysfunction

Erectile dysfunction (ED) is defined as persistent inability to achieve or maintain penile erection sufficient for satisfactory sexual performance (National Institute of Health 1993).

2.2.1. Pathophysiology

Erection is triggered by sexual stimulation in the central nervous system which is signaled via autonomic nerves to the penile corpora cavernosa. Within the penis, the erection begins with relaxation of smooth muscle cells through release of neurotransmitters leading to accumulation of nitric oxide (NO) which in turn leads to vasodilatation of the cavernous artery and helicine arterioles in association with relaxation of the trabecular erectile tissue. As a result, penile blood flow increases several-fold leading to the venous plexuses, located between the sinusoids and rigid tunic covering the penis, to compress and trap blood within the corpora cavernosa enabling normal veno-occlusive function. Shear stress in the arteries

results in further release of endothelial nitric oxide which is a sustaining factor in erection.

ED is commonly classified into seven categories; vasculogenic, neurogenic, anatomical, hormonal, psychogenic, drug-induced and traumatic ED (Hatzimouratidis et al. 2010). The most common cause of organic ED involves impaired vasculature of the penis by several pathophysiological mechanisms, including diminished arterial inflow, endothelial and smooth muscle dysfunction, cavernosal fibrosis and veno-occlusive dysfunction (Nehra et al. 1996, Moreland et al. 1995, Burnett 1997).

The important role of NO-mediated relaxation of smooth muscle cells for penile erection has been extensively studied (Burnett 1997, Bivalacqua et al. 2005, Musicki et al. 2005, Numao et al. 2007). NO is released from cavernosal nerve terminals onto the smooth muscle cells within the media of penile arterial vessels and cavernosal bodies causing them to relax (Rajfer et al. 1992, Burnett 1997). It is believed that ED is mainly caused by a reduction in the bioavailability of neuronal- and endothelial-derived NO (Numao et al. 2007, Musicki et al. 2005, Bivalacqua et al. 2005) . A recent study from Hurt et al highlights the significance of neuronal NO in the maintenance of an erection (Hurt et al. 2012). Furthermore, the reduction of endothelial-derived NO causes imbalance between vasodilating and vasoconstricting modulators in vascular endothelium leading to dysfunction of the endothelium (Shaul et al. 1996, Lerman & Burnett 1992). The well-known association between endothelial dysfunction and CVD (Anderson et al. 1995, H. Cai & Harrison 2000) has supported the hypothesis that the same kind of relationship exists between ED and endothelial dysfunction (Jackson 2008). Several studies have investigated the association between CVD and ED, with suggestions that the onset of ED can predict the development of systemic atherosclerosis, specifically CAD (C. Vlachopoulos et al. 2007, F. Montorsi et al. 2003, Safarinejad 2003, H. A. Feldman et al. 1994). The mechanism behind this association has several possibilities, including narrowing of the penile arteries, a low-grade inflammation and subsequent endothelial dysfunction (Azadzoi et al. 1998, P. Montorsi et al. 2003).

In addition, smooth muscle dysfunction followed by apoptosis and decreased elasticity of the penile supportive structures leads to the venous flow disruption in later phases of ED (Nehra et al. 1996, Moreland et al. 1995). When a man loses approximately 15% of corporal smooth muscle mass, this venous leakage occurs from the penis (Nehra et al. 1996). Venous leakage or cavernosal veno-occlusive dysfunction is common in men with ED, regardless of age (Teloken et al. 2011, Rajfer et al. 1988). The ability to achieve and maintain an erection is a result of a dynamic balance between inflow and outflow of blood within the cavernosal bodies. In ED, this balance is disrupted either by insufficient arterial inflow or

increased venous outflow and it is also associated with blood pressure, which is discussed later in this thesis.

ED is a sum of complex pathophysiological mechanisms where endothelial and smooth muscle cell dysfunction seems to play a crucial role.

2.2.2. Epidemiology

ED is the most common male sexual disorder. It affects all age groups and has a significant impact on quality of life (National Institute of Health 1993, Rosen et al. 2004, H. A. Feldman et al. 1994). Cultural differences, different definitions of ED and population characteristics have a significant impact on prevalence rates of ED. It is projected that, by the year 2025, over 300 million men worldwide will have ED (Ayta et al. 1999).

The Massachusetts Male Aging Study, a landmark community-based study conducted from 1987 to 1989, investigated ED inclusively among 1,709 men 40 to 70 years old (H. A. Feldman et al. 1994). Feldman et al demonstrated that the combined prevalence of minimal, moderate and complete ED was 52% (H. A. Feldman et al. 1994). The follow-up phase of the study was conducted from 1995 to 1997 (Johannes et al. 2000). With an analysis sample consisting of 847 men without ED at baseline, Johannes et al reported that the incidence of ED was 25.9 cases per 1,000 men annually (Johannes et al. 2000).

Since then, several epidemiological studies have reported a broad spectrum of estimations on the prevalence of ED. A population-based study from the Tampere region in Finland, among 50 to 75-year-old men, reported as high as 76.5% overall prevalence rates of ED (Shiri et al. 2003). Moreover, in a study of 2,476 non-institutionalized Spanish men 25 to 70 years old the prevalence of ED was 12.1% and 18.9% according to a single question and the International Index of Erectile Function (IIEF), respectively (Martin-Morales et al. 2001). In a younger population of Brazilian men aged 18 to 40 years, the prevalence of ED, defined by a single question, was as high as 35%, the majority suffering from mild ED (Martins & Abdo 2010). The Global Online Sexuality Survey reported prevalence rates of 45.1% in the Middle East (Shaeer & Shaeer 2011) and 37.7% in the United States (Shaeer & Shaeer 2012).

Recently, Wang and colleagues conducted a large meta-analysis of prevalence of ED in mainland China with a total of 48,254 participants (Wang et al. 2017). The pooled prevalence of ED in men was about 50% (Wang et al. 2017). The occurrence rates of ED in age groups 40 to 49, 50 to 59 and 60 to 69 were 40%, 60%, and 79%, respectively (Wang et al. 2017). Furthermore, the prevalence rates reported by different diagnostic methods were 14% for self-reports and 50% for the IIEF-5 (International Index of Erectile Function-5) (Wang et al. 2017).

2.2.3. Symptoms and diagnosis

Most men have problems with erections from time to time. But when a man is regularly unable to achieve or maintain an erection firm enough for sexual intercourse, ED is present. It is common that men with these symptoms seek help from their own primary care physician. Sometimes, especially with older men, an underlying health condition can be found, primarily a cardiovascular one, which needs attention and treatment. Because of this, the significance of primary care in treating and diagnosing ED is important.

The cornerstone in the diagnosis of ED is to obtain a comprehensive and accurate sexual and medical history of the patient, including relevant drug, tobacco and alcohol use and psychosocial status (Shamloul & Ghanem 2013). The initial assessment in a primary care setting should also include focused physical examination (penile, scrotal and prostate examination) and selected laboratory tests (The Process of Care Consensus Panel 1999). Because of the established association between ED and cardiovascular disease, the evaluation of other vascular beds should be considered (H. A. Feldman et al. 1994, Dong et al. 2011, Blumentals et al. 2003).

Standardized questionnaires, being non-invasive and easy-to-use, are commonly used to define ED and to measure its severity. However, there are some weaknesses with questionnaires, such as the inability to evaluate the etiology of the ED, and to take into account the respondent´s personal and cultural backgrounds (Blander et al. 1999). One of the most practical and frequently used questionnaires is the International Index of Erectile Function (IIEF) (Rosen et al. 1997). Primarily to assess the efficacy endpoint in randomized controlled trials of ED, Rosen et al developed this self-administered, cross-culturally valid and psychometrically sound measure of erectile function for research or clinical purpose (Rosen et al. 1997). It consists of 15 items addressing the relevant domains of male sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction). Each question is graded on a 5-point scale in which lower scores represent more severe ED, providing the opportunity to examine dose-response effects. In 1999, a shorter version of the IIEF, The International Index of Erectile Function short form (IIEF-5), was constructed by the same authors (Rosen et al. 1999). This questionnaire, with the same 5-point grading scale, uses four questions from the sexual function domain and a single question from the intercourse satisfaction domain of the original IIEF (Table 1).

Different types of objective tools for measuring and evaluating the erectile function have been introduced over the years, such as the penile duplex ultrasound, cavernosography and nocturnal penile tumescence testing (Lue et al. 1989, Kessler 1988). There have also been attempts to create sophisticated tools to assess male sexual dysfunction from the neurophysiological point of view. Bulbocavernosus

reflex latency time, pudendal somatosensory evoked potentials, and sympathetic skin responses have been considered as possible candidates for the diagnosis and evaluation of ED (Ertekin et al. 1985, Opsomer et al. 1986, Curt et al. 1996). All these tests are expensive, time-consuming, invasive, and rarely conclusive except in experienced hands (F. Giuliano & Rowland 2013).

Table 1. The IIEF-5 questionnaires. The score is the sum of the responses to the five items, ranging from 5 to 25. Reprinted with permission from Springer Nature, Rosen et al Int J Impot Res. 1999 Dec;11(6):319-26.

Over the past six months:						
1	How do you rate your **confidence** that you could get and keep an erection?	Very low	Low	Moderate	High	Very high
		1	2	3	4	5
2	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never/never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/always
		1	2	3	4	5
3	During sexual intercourse, **how often** were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/never	A few times (much less than half the time)	Sometimes (about half the time)	Most time (much more than half the time)	Almost always/always
		1	2	3	4	5
4	During sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
		1	2	3	4	5
5	When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/always
		1	2	3	4	5

2.2.4. Risk factors

Several epidemiological studies have demonstrated that age is the primary risk factor for ED (Shiri et al. 2003, Wang et al. 2017, El-Sakka 2007, Martin-Morales et al. 2001, H. A. Feldman et al. 1994). The prevalence and severity of ED increases with age (Shiri et al. 2003, El-Sakka 2007, Martin-Morales et al. 2001, Wang et al. 2017, H. A. Feldman et al. 1994). Martin-Morales et al. reported with a total of 2,476 non-institutionalized men 25 to 70 years old that a strong relationship exists between the subject´s age and frequency or severity of ED, defined by either a simple self-assessment question or the IIEF (Martin-Morales et al. 2001). Therefore, epidemiological studies concentrating on ED should always consider age as a confounding factor.

Diabetes mellitus seems to be the second most common risk factor for ED. This association was established for the first time in 1958 by Rubin and Babbot (Rubin & Babbott 1958). Among diabetic patients, ED occurs three times more frequently compared to non-diabetics (49.3% vs 15.6%) (Ponholzer et al. 2005) and the prevalence ranges from 35% to 90% (El-Sakka & Tayeb 2003, Sasaki et al. 2005, McCulloch et al. 1980, F. A. Giuliano et al. 2004). Diabetes was also one of the strongest comorbid conditions associated with ED (RR 1.5), in a large cross-

sectional study, The Health Professionals Follow-up Study, with 31 742 men, aged 53 to 90 years (Bacon et al. 2003). Moreover, men with diabetes seem to develop ED 10 to 15 years earlier than the average ED patient (H. A. Feldman et al. 1994). The Diabetes Control and Complications Trial randomized 761 men with type I diabetes into intensive and conventional glycemic control groups in the 1980s (Wessells et al. 2011). At the 10-year follow-up, the men in the intensive glycemic control group had significantly lower rate of ED (12.8% vs. 30.8%) (Wessells et al. 2011). Recently, Binmoammar et al reviewed systematically five cross-sectional studies and reported that impaired glycemic control in patients with type II diabetes contributes significantly to the development and severity of ED (Binmoammar et al. 2016). In contrast, there are no data available on the possibility that erectile function could be improved with stricter glycemic control. As the duration of diabetes is associated with ED, it is natural that also diabetic complications correlate with higher risk of ED, such as retinopathy (OR 2.06) (S. K. Chew et al. 2013), microalbuminuria (OR 2.5) (Chuang et al. 2012) and neuropathy (OR 2.04) (Sasaki et al. 2005).

It is well known that smoking induces oxidative stress (Peluffo et al. 2009), causes endothelial dysfunction (Celermajer et al. 1993) and impairs nitric oxide pathways (Imamura et al. 2007). Although the pathophysiology between smoking and ED is unclear, it is generally accepted that smoking causes ED. The association has been demonstrated in several cross-sectional and prospective studies (H. A. Feldman et al. 2000, J. He et al. 2007, Bacon et al. 2003, Blanker et al. 2001). Smokers, compared to nonsmokers, have increased risk of ED, that varies from 1.4 to 2.4 (Blanker et al. 2001, Austoni et al. 2005, Wu et al. 2012, Safarinejad 2003). A literature review of 18 studies by Dorey confirmed the harmful effect of smoking on erectile function (Dorey 2001). Smokers were 1.5 times more likely to suffer ED than non-smokers (Dorey 2001). A prospective study from the Massachusetts Male Aging Study reported with 513 men, that cigarette smoking at baseline almost doubled the likelihood of moderate or complete ED at follow-up (24% vs 14%, adjusted for age and covariates) (H. A. Feldman et al. 2000). Interestingly, passive smoking also significantly predicted incident ED (H. A. Feldman et al. 2000). In addition, Chew et al reported that the relationship between smoking and ED seems to be dose-dependent and cumulative, although the age-adjusted odds of ED among current smokers was not statistically significant (K. K. Chew et al. 2009). The literature regarding the effect of smoking cessation on ED is controversial. In several studies, current and ex-smokers tend to have similar risk rates for ED, underestimating the risk reduction of smoking cessation (Safarinejad 2003, K. K. Chew et al. 2009). Guay et al performed a nocturnal penile tumescence tests in ten currently smoking men before and after 24 hours of smoking cessation (Guay et al. 1998). Improvement in erection was demonstrated within 24 hours. Another study by Pourmand et al investigated the association between smoking cessation with nicotine replacement therapy and ED (defined by IIEF-5 score)

(Pourmand et al. 2004). At one-year follow-up, the men who were able to stop smoking had their IIEF-5 score improved by a quarter. However, none of the men who suffered from severe ED experienced any improvement (Pourmand et al. 2004).

The relationship between essential hypertension and ED is well established (Javaroni & Neves 2012, Roth et al. 2003, Doumas & Douma 2006, Viigimaa et al. 2011, Burchardt et al. 2000). It is even hypothesized that the pathophysiology of these two disorders is the same (Bansal 1988, Clavijo et al. 2014). However, there are numerous overlapping comorbid conditions and risk factors influencing this relation (Doumas & Douma 2006). Compared to the general population, hypertensive patients have a higher prevalence of ED (H. A. Feldman et al. 1994, Burchardt et al. 2000). This increased age-adjusted relative risk of ED among hypertensive patients ranges from 1.3 to 6.9 (Bacon et al. 2003, Ponholzer et al. 2005, Martin-Morales et al. 2001, Shiri et al. 2003). However, a significant limitation exists in the majority of these studies. The definition of hypertension frequently relies on self-reporting, not on an actual measurement of blood pressure. In 2006, Doumas et al demonstrated with 358 hypertensive and 276 normotensive men without prior diabetes or CVD, that duration and severity of hypertension, anti-hypertensive medication, and age were positively correlated with ED (Doumas et al. 2006). In a population-based study by Wu et al with 2,686 participants, a history of hypertension (defined as RR≥140/90 and/or the use of antihypertensive medications) increased the risk of ED, but was not statistically significant after adjustment for other variables (Wu et al. 2012). In a more detailed investigation into the relation of blood pressure and ED, Kakkavas et al assessed ED in 174 consecutive men with untreated, newly diagnosed essential hypertension (Kakkavas et al. 2013). In their study population, both 24-h ambulatory and office DBP were lower in the ED group, but the results were not statistically significant. It has been suggested that increased blood pressure induces endothelial dysfunction and damage to smooth muscle cells (C. Vlachopoulos et al. 2008, Toblli et al. 2000). Anti-hypertensive medicines, such as thiazide diuretics and beta blockers, in their own right bring a contributing factor to the relationship between hypertension and ED (Grimm et al. 1997, Cordero et al. 2010). Baumhäkel et al reviewed 14 randomized controlled trials (RCTs) which evaluated the effect of different cardiovascular drugs on ED and concluded that only thiazide diuretics and beta-blockers, except nebivolol, may adversely influence erectile function (Baumhakel et al. 2011).

Conflicting results from several observational studies have been reported for (Martin-Morales et al. 2001, Safarinejad 2003, Mirone et al. 2004) and against (Bacon et al. 2003, Selvin et al. 2007, Wu et al. 2012) the association between dyslipidemia and ED. Only few longitudinal studies have addressed the relationship between hyperlipidemia and ED (Wei et al. 1994, H. A. Feldman et

al. 2000, Fung et al. 2004). Fung et al reported 25-year follow-up data from the Rancho Bernardo Study. On multivariate analysis, categorically defined hypercholesterolemia was an independent predictor of ED (OR 1.9) and the most frequent single risk factor (present in 55%) among 570 Caucasian men (Fung et al. 2004). In a more short-term follow-up study (mean 22 months), Wei et al reported, that every 1 mmol/l of increase in TC was associated with 1.32 times the risk of ED and every 1 mmol/l of increase in HDL-C was associated with 0.38 times the risk (Wei et al. 1994). In the Massachusetts Male Aging Study, HDL-C showed an inverse relation to ED at baseline among the older half of the cohort (H. A. Feldman et al. 1994), but no significant association between HDL-C or TC and incident ED was found in the follow-up study (H. A. Feldman et al. 2000). Statins are the first-line medical therapy for hyperlipidemia. The effect of statins on ED has been reviewed by two separate meta-analyses in 2014 (X. Cai et al. 2014, Kostis & Dobrzynski 2014). Kostis and Dobrzynski combined 11 studies and observed 3.4-point increase in IIEF-5 scores compared to controls (Kostis & Dobrzynski 2014). It is worth noting that the majority of these studies reported negative results regarding the association between statins and ED. The other meta-analysis by Cai et al reviewed seven RCTs and found a significant 3.27-point increase in IIEF-5 scores (X. Cai et al. 2014).

Most studies have confirmed the positive effect of physical activity on ED. An 8-year follow-up report from the Massachusetts Male Aging Study concluded, with 593 men without prior history of ED, diabetes or heart disease, that physical activity may reduce the risk of erectile dysfunction even if initiated in midlife (Derby et al. 2000). Consistent with this, Cheng et al published a comprehensive meta-analysis of 11 studies, demonstrating the protective nature of increased physical activity on ED (Cheng et al. 2007). Rosen et al supported these findings among type 2 diabetics (Rosen et al. 2009). Low physical activity is closely linked to obesity, which is often coexistent with diabetes and hypertension. A well designed RCT by Esposito et al conducted a two-year lifestyle intervention that addressed physical activity and caloric restriction in 110 healthy obese Italian men with ED (Esposito et al. 2004). The 55 men in the intervention group attended monthly sessions designed to achieve a sustained and long-term reduction in body weight (≥10% of initial weight maintained for 2 years) and an increase in physical activity. The men in the control group received general information regarding exercise and diet. After the two years, men in the intervention group had significantly increased their physical activity and improved their erectile function from baseline, as compared with the control group. Over 30% of the participants regained their erectile function in the intervention group during the trial.

Testosterone is essential for penile erection by generating sufficient intracavernosal pressure and smooth muscle function (Bivalacqua et al. 1998). The prevalence of hypogonadism among men with ED seems to vary from 23% to 36%

(Tsertsvadze et al. 2009) but is influenced dramatically by the adopted threshold level of testosterone (Kohler et al. 2008). In addition, the European Male Aging Study reported that the association between free testosterone levels and ED was threshold-dependent on total testosterone levels (≤8 nmol/liter) (O'Connor et al. 2011). The relationship between testosterone and ED has commonly been addressed in several studies through the association between testosterone replacement treatment and ED. In 2014, a systematic review by Isidori et al concluded from 20 RCTs, that a mean improvement of 4.32 points in the IIEF-5 scores was caused by testosterone replacement treatment (Isidori et al. 2014). They also reported that no effect of testosterone replacement treatment on ED was demonstrated in men with testosterone levels over 12 nmol/liter (Isidori et al. 2014). A recently published multicenter Testosterone Trial demonstrated in symptomatic men 65 years of age or older, that testosterone replacement treatment has a positive impact on overall sexual function (Snyder et al. 2016) . Men in the testosterone group increased their IIEF scores by 2.64 points. In summary, the effect of hypogonadism on erectile function is complex and needs further investigation. In primary care it would be recommendable, that all men with ED should have their testosterone levels checked. The initiation of testosterone replacement treatment should be made by a urologist or physicians specialized in ED and hypogonadism, as such decisions will also require knowing the risks of testosterone treatment.

There is a reasonable amount of evidence on the association between depression and ED (Mak et al. 2002, Martin et al. 2014, Araujo et al. 1998, Korhonen et al. 2015). However, it is not always clear which is the precedent condition. In addition, ED is a common side effect of selective serotonin reuptake inhibitors, which are the most frequent drugs used for treating depression (Serretti & Chiesa 2009). Araujo et al reported from the Massachusetts Male Aging Study that men suffering from depressive symptoms are about twice as likely to have ED as the general population (Araujo et al. 1998). Mak et al came to the same conclusion with 799 Belgian men. Moreover, a five-year prospective study conducted in Australia demonstrated that depressed men at baseline were 2.5 times more likely to develop ED (Martin et al. 2014).

2.2.5. Erectile dysfunction and peripheral arterial disease

ED and PAD share similar risk factors, including age, smoking, diabetes, hypertension, dyslipidemia and are both associated with high risk of cardiovascular events and mortality(Fowkes et al. 2013, H. A. Feldman et al. 1994, Dong et al. 2011). Montorsi et al even hypothesized that these two ailments, including CAD and CBVD, could be manifestations of the same systemic vascular disease (P. Montorsi et al. 2003, P. Montorsi et al. 2005). This “artery size hypothesis” was introduced by them, suggesting that atherosclerosis, a well-known

systemic disorder, affects all major vascular territories to the same extent, but the penis, having the smallest arteries in diameter compared to coronary or femoral arteries, would be affected the earliest (P. Montorsi et al. 2003, P. Montorsi et al. 2005), thus presenting ED as an early sign of vascular disease. Other underlying mechanisms that could link ED with PAD or other CVDs are endothelial dysfunction and smooth muscle dysfunction (Kirby et al. 2005, Kaiser et al. 2004).

The relationship between ED and CVD was introduced by Tuttle et al in the 1960s, when they interviewed relatively young male patients with a history of myocardial infarction and reported that 10% of them were impotent (Tuttle et al. 1964). This finding was later confirmed by Feldman et al in the Massachusetts Male Aging Study, reporting 29% higher prevalence of ED among men with treated heart disease compared to the entire sample (H. A. Feldman et al. 1994). After that, several cross-sectional and prospective studies have investigated this association, demonstrating mainly positive correlations (C. Vlachopoulos et al. 2005, Ponholzer, Temml, Obermayr et al. 2005, Thompson et al. 2005, Hotaling et al. 2012). In 2011, Dong and colleagues published a meta-analysis of prospective cohort studies with a goal to evaluate the association between ED and CVD and all-cause mortality (Dong et al. 2011). Combined RRs for men with ED compared to the reference group in twelve studies with 36,744 participants were 1.48 for CVD and 1.19 for all-cause mortality (Dong et al. 2011). Two years later Vlachopoulos et al set the same goal and conducted a similar meta-analysis with 16 longitudinal studies, including 10 studies from the earlier meta-analysis (C. V. Vlachopoulos et al. 2013). The analysis demonstrated that ED predicted cardiovascular events (RR 1.44) and all-cause mortality (RR 1.25) especially among younger subjects. However, cardiovascular death did not correlate significantly with ED.

There are a moderate number of studies describing the association between ED and PAD with conflicting results (Polonsky et al. 2009, Banks et al. 2013, Lahoz et al. 2016, Chai et al. 2009, D. I. Feldman et al. 2016, Blumentals et al. 2003). A retrospective database study by Blumentals et al, included a total of 12,825 ED patients and an equal number of male patients without ED (Blumentals et al. 2003). The cohort of men with ED were noted to have a 75% increase in risk for perivascular disease after adjusting for age at ED diagnosis, smoking, obesity and use of ACE inhibitors, beta blockers and statins (Blumentals et al. 2003). A positive correlation was also found in a prospective study with 95,038 randomly sampled men from the general population of New South Wales, Australia (Banks et al. 2013). In these men, moderate and severe ED was associated with 1.6 to 2.7 increased risk of PAD (Banks et al. 2013). In a more selective study population of 623 men referred for cardiac stress testing, increasing severity of ED was associated with elevated risk of asymptomatic PAD, defined by ABI $\leq$ 0.90 (Polonsky et al. 2009). In addition, Chai et al evaluated 185 elderly men (mean age

71 years) from the Rancho Bernardo Study and reported that lower toe-brachial index was associated independently with the severity of ED, defined by the IIEF-5 questionnaire (Chai et al. 2009). However, not all the studies have been able to demonstrate a correlation between ED and PAD. Recently, two papers with opposite results on the link between ED and ABI have been published (D. I. Feldman et al. 2016, Lahoz et al. 2016). In 614 Spanish men (mean age 61 years) derived from the general population, the presence of ED, defined by IIEF-5, was not associated either with the mean ABI or the prevalence of men with ABI < 0.9 (Lahoz et al. 2016). However, there was a trend towards a lower ABI with increasing ED severity (Lahoz et al. 2016). Feldman et al reported from the Multi-Ethnic Study of Atherosclerosis, including 1862 men, that all the other abnormal subclinical vascular disease measures except low ABI were strongly associated with ED in the unadjusted model (D. I. Feldman et al. 2016). In the fully adjusted models only coronary artery calcium and carotid plaque score remained significant factors (D. I. Feldman et al. 2016).

In summary, the data concerning the relationship of ED and PAD are not conclusive, and therefore, more epidemiological and especially longitudinal studies are needed to address the issue.

3. AIMS OF THE STUDY

This thesis was designed to investigate the associations between cardiovascular risk factors and peripheral arterial disease focusing on men in a primary care setting. The aims in detail were the following:

1. To investigate factors affecting the progression of PAD in borderline ABI subjects, who underwent a multifactorial cardiovascular intervention.
2. To assess the relationship between height and PAD, in a population at risk for cardiovascular disease
3. To investigate the association between PAD and ED in a male cardiovascular risk population.
4. To characterize the relationship between blood pressure and ED in detail.

4. MATERIALS AND METHODS

4.1. Study population

The study population consisted of individuals who took part in a large community-based survey, Harjavalta Risk Monitoring for Cardiovascular Disease (the Harmonica Project). This study was carried out in the towns of Harjavalta (7646 inhabitants on 31 December 2007) and Kokemäki (8217 inhabitants on 31 December 2007) in the southwest of Finland from August 2005 to September 2007 (Korhonen, Jaatinen et al. 2009). An invitation to the project was mailed to 6013 community-dwelling inhabitants aged 45 to 70 years, including a cardiovascular risk factor survey, a tape for the measurement of waist circumference, and a type 2 diabetes risk assessment form (FINDRISC, Finnish Diabetes Risk Score) (Lindstrom & Tuomilehto 2003).

The subjects were asked to report their waist circumference, most recent BP, use of antihypertensive medication, history of gestational diabetes or hypertension, and history of coronary heart disease, myocardial infarction, or stroke of their parents or siblings in the risk factor survey. The participation rate was 74%. Those who had at least one cardiovascular risk factor or FINDRISC ≥12 in Harjavalta or ≥15 in Kokemäki were invited for laboratory tests (oral glucose tolerance test and plasma lipids) and physical examination performed by a trained nurse, including measurements of height, weight, BMI, waist circumference and blood pressure. The enrolment examination also included generic health surveys, and medical history. In this stage of the project there were 1469 participants from Harjavalta and 1283 participants from Kokemäki. Attendance and all the tests included were free of charge for the subjects.

If the test results revealed hypertension, diabetes, impaired glucose tolerance, metabolic syndrome, body mass index ≥30 kg/m^2, or a 10-year risk of CVD death of 5% or more according to the Systematic Coronary Risk Evaluation system (SCORE) (Conroy et al. 2003), the study nurse gave healthy lifestyle information to all subjects personally and scheduled an appointment with a physician after 2-4 months. During this time the plasma lipids and fasting glucose were retested. A single physician examined these high risk persons, assessed target organ damage, and in Harjavalta, measured ABI from 1076 subjects. Subjects with intermittent claudication, previously diagnosed diabetes, cardiovascular or renal disease were excluded from the data analysis of this thesis. The final cohort of study II included 972 subjects. Only the male subjects with properly filled IIEF-5 questionnaire and no previously diagnosed cancer or neurological disease (Parkinson´s disease, multiple sclerosis) were included in studies III and IV, yielding analytic cohorts of 380 and 665 male subjects, respectively. In addition, in study IV, subjects with

established hypertension or having antihypertensive medication were also excluded. The formation of the study population is demonstrated in Figure 6.

The study subjects were assigned to receive conventional treatment for multiple risk factors of CVD. Treatment goals were set according to the 2003 European guidelines on CVD prevention in clinical practice (De Backer et al. 2003). All the study subjects were given exercise instructions recommending physical activity for at least 30 minutes per day or four hours per week. Subjects with a smoking habit were given motivational counselling and prescribed an optional antismoking medication (bupropion hydrochloride). Dietary intervention was given for study subjects with BMI ≥ 25 kg/m2.They were set a goal for at least 5% weight reduction by reducing saturated fat in their diet. The goal for blood pressure was set under 140/90mmHg and for newly diagnosed diabetics (n=10) under 130/80 mmHg. Arterial hypertension was treated primarily with ACE inhibitors or angiotensin II-receptor antagonists and secondarily with calcium-channel blockers, thiazides or beta-blockers. Statin was prescribed for hypercholesterolemia; for the high risk subjects the TC and LDL-C goal was set at < 4.5mmol/l and < 2.5 mmol/l, respectively, and for the rest of the study cohort at <5.0 mmol/l and < 3.0 mmol/l (De Backer et al. 2003), respectively.

The borderline ABI follow-up study (Study I)

The study subjects with borderline ABI (0.91 - 1.00) (n=193) at baseline were invited to attend the seven-year follow up visit. Participation rate was 64% (n=123). A modified questionnaire, laboratory tests and ABI measurements were repeated for them. The protocol for ABI measurement was the same as at baseline. The reasons for not attending the follow-up were withdrawal (n=48), moving to a new district (n=16) and death (n=6).

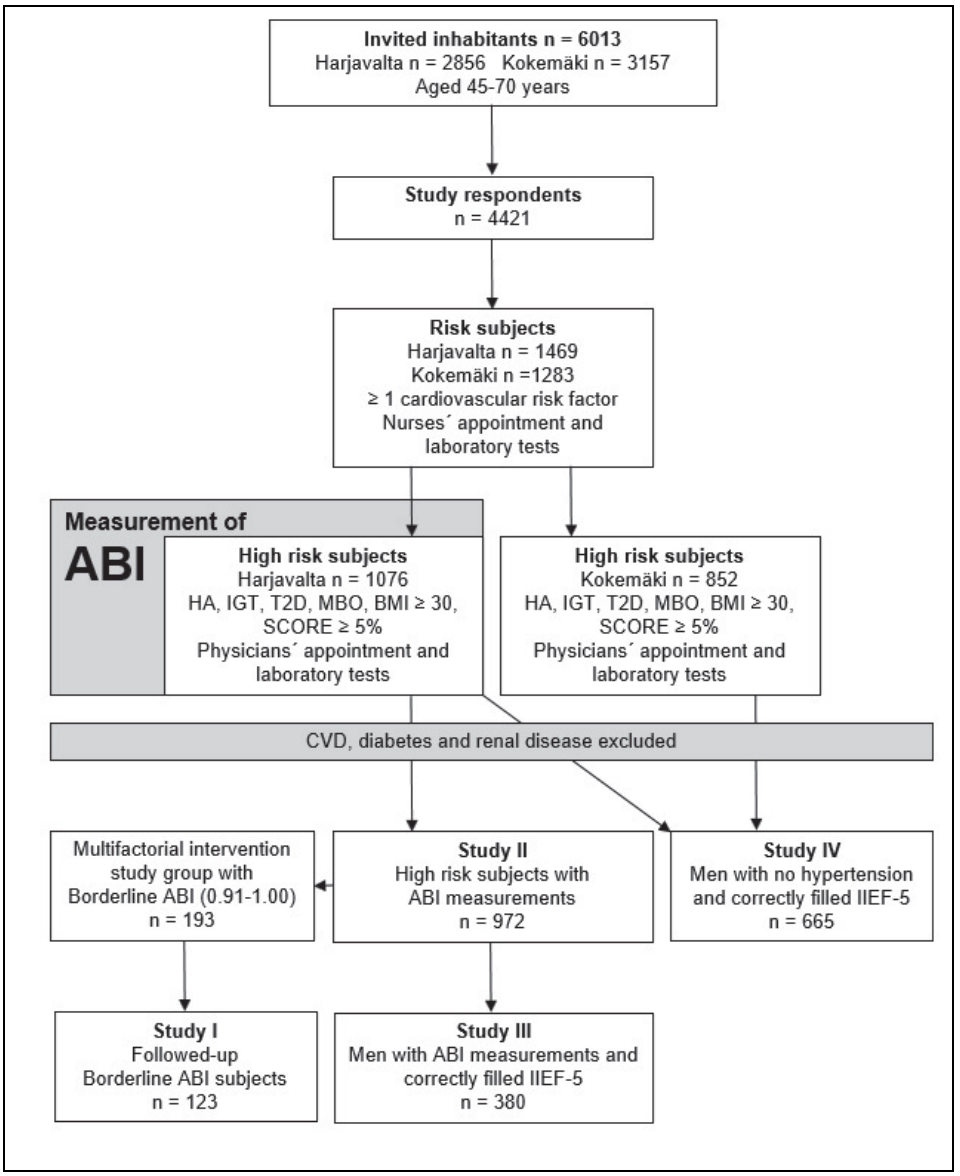

Figure 6. *Selection of the study population. ABI, ankle-brachial index; BMI, body mass index; HA, hypertension arterialis; IGT, impaired glucose tolerance; MetS, metabolic syndrome; SCORE, Systematic Coronary Risk Evaluation system; T2D, type 2 diabetes. CVD, cardiovascular disease*

4.2. Methods

4.2.1. Ankle-brachial index measurement

Systolic blood pressure (SBP) measurements for calculation of the ABI were obtained using appropriate-sized BP cuffs and Doppler instrument (UltraTec®

PD1v with a vascular probe of 5 MHz; Medema T/A Omega Medical Supplies Ltd., UK). The BP cuff was applied over the brachium and just above the malleoli. SBPs were measured once in all four limbs, from the brachial and dorsalis pedis arteries with the patient in a supine position. If the dorsalis pedis pulse was not detected at the baseline examination, the posterior tibial artery pulse was used. ABI was calculated by dividing the lower ankle SBP with the higher brachial SBP. At the baseline examination ABI was measured by a single doctor and at the follow-up examination by two trained nurses. The protocol for ABI measurement was the same as at baseline.

A participant with ABI ≤ 0.90 in either leg was categorized as having PAD. Subjects with an ABI between 0.91 and 1.00 were considered as borderline ABI patients. Normal ABI was defined as 1.01–1.40. In subjects with ABI higher than 1.40 this was categorized as abnormally high ABI due to non-compressible tibial arteries (Aboyans et al. 2012).

4.2.2. Blood pressure measurement

A trained nurse measured BP with a calibrated mercury sphygmomanometer with subjects in a sitting posture, after resting for at least five minutes with the cuff placed on the arm. Depending on the circumference of the arm, an appropriate sized cuff was used. In each participant, the mean of two BP readings taken at intervals of at least two minutes was used in the study. Subjects were provided with and taught to use an automatic validated BP device (Omron® M4-1, the Netherlands) for home BP monitoring, if the nurse measured the mean SBP ≥140 mmHg or the mean DBP ≥90 mmHg and the subject had no previously diagnosed hypertension. These subjects were given instructions to take duplicate BP measurements in a sitting position after five minutes of rest in the morning and evening for one week. As recommended by the guidelines of the European Society of Hypertension, the mean home BP was then calculated from the recorded measurements excluding the first day (Parati et al. 2008). Participants were defined as hypertensive if they used antihypertensive medication, or their mean SBP was ≥135 mmHg or mean DBP was ≥85 mmHg in the home BP monitoring (Parati et al. 2008). Pulse pressure was calculated by subtracting the mean DBP from the mean SBP.

4.2.3. Anthropometric measurements

Height and weight were measured with the participants in standing position without shoes and outer garments. Height was recorded to the nearest 0.5 cm and weight to the nearest 0.1 kg. Waist circumference was measured at the midway level between the lower rib margin and the iliac crest. BMI was calculated as weight (kg) divided by the square of height in meters (kg/m^2).

4.2.4. Erectile dysfunction

The International Index of Erectile Function 5-item questionnaire (IIEF-5) (Rosen et al. 1999) was used to assess ED. All men reporting a zero score on any of the questions or leaving any question unanswered were excluded. In study III IIEF-5 scores of 5-16 were considered to represent moderate to severe ED, and scores ≥ 17 mild ED or normal erectile function (Rosen et al. 1999). In study IV, scores ≥ 21 were defined as normal erectile function and no severity grading was carried out.

4.2.5. Physical activity

Leisure-time physical activity (LTPA) was assessed by a non-validated questionnaire at baseline and follow-up. In study I and II, LTPA was defined as follows; high LTPA ≥ 30 minutes exercise at a time for at least 4 times a week, moderate LTPA ≥ 30 minutes exercise at a time from one to three times a week, and low LTPA ≥ 30 minutes exercise randomly or never. In study III and IV, LTPA was categorized as follows: high LTPA for ≥ 30 minutes at a time for six or more times a week; moderate LTPA for ≥ 30 minutes at a time for four to five times a week; low LTPA for ≥ 30 minutes at a time for maximum of three times a week.

4.2.6. Intermittent claudication

At the baseline survey, intermittent claudication was ruled out with the specific question ´Have you experienced exertional pain localized to the calf or thigh or buttocks, which stops you walking and is relieved by rest? ´. At the follow-up, the Edinburgh Claudication Questionnaire was used to define intermittent claudication.

4.2.7. Laboratory measurements

Laboratory tests were carried out using blood samples, which were obtained after at least 12 hours of fasting. TC, HDL-C, and triglycerides (TG) were measured enzymatically (Olympus® AU640, Japan). Friedewald formula was used to calculate LDL-C. Fasting glucose values were measured from capillary whole blood using the HemoCue® Glucose 201+ system (Ängelholm, Sweden), which converts the result to plasma glucose values. Plasma potassium and sodium were measured with the indirect ion-specific electrode method (Olympus® AU640, Japan). High-sensitivity CRP was assayed using a microparticle enhanced turbidometric method on a Konelab® 60i analyzer (Thermo Electron, Finland). Oral glucose tolerance test (OGTT) was initiated by measuring capillary fasting plasma glucose and a 2-hour plasma glucose after ingestion of 75 g of anhydrous glucose dissolved in water.

Glucose disorders were defined according to the updated World Health Organization (WHO) criteria (WHO Diabetes 2006). Based on 2-hour plasma glucose, participants were categorized into newly diagnosed diabetes, impaired glucose tolerance and normal glucose tolerance if their 2-hour plasma glucose concentrations were ≥12.2, 8.9–12.1, and <8.9 mmol/l, respectively. Based on fasting plasma glucose alone, participants were categorized into newly diagnosed diabetes, impaired fasting glucose and normal fasting glucose, using threshold levels of ≥7.0, 6.1–6.9 and ≤6.0 mmol/l, respectively.

4.2.8. Other lifestyle habits

Other self-administered questionnaires were also completed by the subjects, including questions about sociodemographic factors, occupational status and smoking status. Cohabiting was categorized into groups of single, married, living with partner, separated/divorced and widowed. Occupational status was categorized as full-time employed, unemployed, part-time retired and retired. Smoking status was categorized as never smokers, current smokers and former smokers. Beck´s Depression Inventory (BDI) was used to screen depressive symptoms (Beck et al. 1961). Scores lower than 10 were considered as sign of no depressive symptoms (Koponen et al. 2010). Participants also filled in the Alcohol Use Disorders Identification Test (AUDIT) (Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG 2001). Alcohol use disorder was defined with a cut-off value of 8 (Reinert & Allen 2007).

4.2.9. Statistical analyses

The data are presented as means with standard deviations (SD) or as counts with percentages. STATA 13.1, StataCorp LP (College Station, TX, USA) statistical package was used for the analyses. In each statistical analysis $p < 0.05$ was considered as statistically significant.

Study I

Statistical comparisons between groups were made using analysis of variance (ANOVA) and chi-square test when appropriate. In the case of violation of the assumptions (non-normality), a bootstrap-type test was used. Statistical comparison of changes in ABI was performed using the bootstrap type paired t-test. To determine the predictors of change in ABI, multivariate ordered logistic regression analysis was applied. Correlation coefficients were calculated by the Pearson method and 95 percent confidence intervals (95% CI) were obtained by bias-corrected bootstrapping (5000 replications).

Study II

The linearity across the quartiles of height was tested using the Cochran-Armitage test and analysis of variance (ANOVA). Adjusted odds ratios (ORs) (95% CIs) were estimated using logistic regression models. The bootstrap method was used when the theoretical distribution of the test statistics was unknown or in the case of violation of the assumptions (e.g. non-normality). The normality of the variables was tested using the Shapiro-Wilk W test.

Study III

Statistical comparisons between subjects without ED and with ED in characteristics were made by using chi-square test, t-test or permutation test. A possible nonlinear relationship risk of ED was assessed by using 5-knot restricted cubic spline logistic regression model. The length of the distribution of knots were located at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. The normality of the variables was tested by using the Shapiro-Wilk W test.

Study IV

Statistical comparisons between subjects without ED and with ED in characteristics were made by using the chi-square test or t-test. The normality of the variables was tested using the Shapiro-Wilk W test. To model the nonlinear relationship between BP levels and ED, a restricted cubic spline (RCS) logistic model procedure was adopted with adjustment for age, cohabiting status, education, fasting plasma glucose, waist circumference and depressive symptoms. The U-shaped relationship between DBP and ED was tested using the Lind and Mehlum method (Lind JT 2010).

4.2.10.Ethical issues

The ethics committee of Satakunta Hospital District approved the study on October 3rd 2005. All the participants provided written informed consent to participate in the project and subsequent medical research.

5. RESULTS

5.1. Physical activity and peripheral arterial disease (I)

The first study of this thesis was the only one with a prospective design. A total of 193 borderline ABI (0.91 - 1.00) subjects at baseline were invited to attend the seven-year follow up visit and sixty-four percent of them participated (n=123). For the whole cohort, the mean ABI was 0.97 ± 0.03 at baseline and 1.01 ± 0.12 at the follow-up visit. The mean ABI increased 0.04 (95% CI: 0.03 – 0.07) (p <0.001) during the follow-up. ABI improved significantly in 25 (20%) subjects (increased ABI group) and 15% (n=18) of the study subjects developed PAD during the follow-up (incident PAD group). The incidence of PAD was 22 (95% CI: 13 – 34) per 1000 person-years. Among eighty subjects (65%) the ABI did not change significantly during the follow-up (stable ABI group). Figure 7 illustrates the ABI values individually at baseline and follow-up. Baseline ABI did not associate with the change in ABI [- 0.12 (95% CI -0.29 to 0.06)]. None of our study subjects had an ABI above 1.40 at baseline or at the follow-up visit.

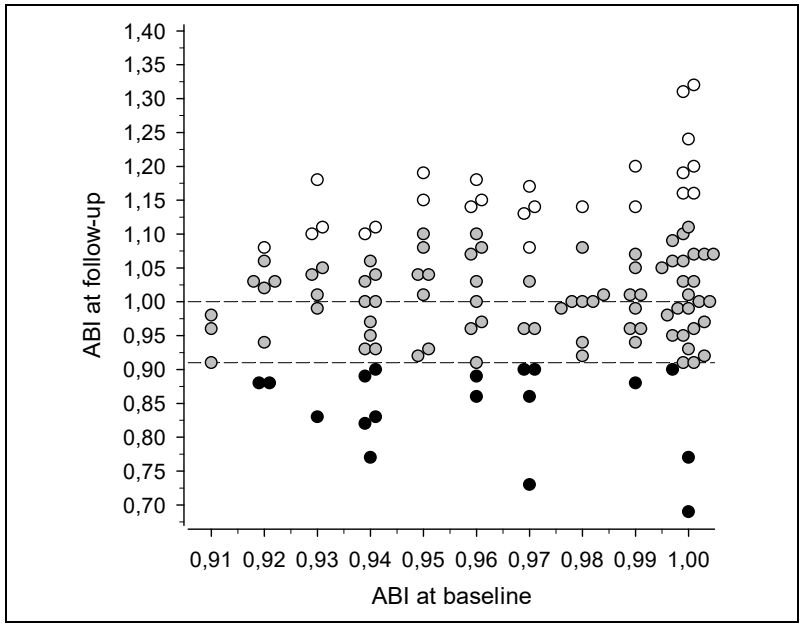

Figure 7. *Ankle-brachial index (ABI) of the study subjects at baseline and follow-up*
○ *Increased ABI = ABI change ≥ 0.15*
◍ *Stable ABI = ABI change < 0.15*
● *Incident PAD = ABI ≤ 0.90*
(Study I: Heikkilä A, et al. Ann Vasc Surg. 2016 Apr; 32:50-6.)

We analyzed the baseline characteristics by the three groups (incident PAD, stable ABI and increased ABI) according to the change in ABI during the follow-up (Table 2). The incident PAD and stable ABI groups included more women than men, and HDL-C level was especially high in the stable ABI group. There was a trend towards higher BMI in the incident PAD group. Physical inactivity was significantly more common in the incident PAD group (39%) compared to the stable ABI group (10%) and increased ABI group (0%) (p=0.003).

Table 2. Baseline characteristics by incident PAD, Stable ABI and Increased ABI subjects

Characteristic	Incident PAD (n=18)	Stable ABI (n=80)	Increased ABI (n=25)	p
Age, y	59.2 (6.6)	58.8 (6.5)	59.3 (6.9)	0.93
Male sex, n (%)	7 (38.9)	25 (31.3)	15 (60.0)	0.036
Body mass index, kg/m²	31.9 (7.8)	28.8 (5.2)	28.4 (3.6)	0.064
Current smoker, n (%)	4 (22.2)	17 (21.3)	3 (12)	0.57
ABI	0.96 (0.027)	0.97 (0.029)	0.97 (0.027)	0.34
Fasting glucose, mmol/l	5.77 (0.60)	5.56 (0.88)	5.60 (0.70)	0.49
2-hour glucose, mmol/l	6.19 (0.79)	5.94 (0.89)	5.73 (0.61)	0.10
Systolic blood pressure, mmHg	146 (17)	155 (18)	152 (19)	0.10
Diastolic blood pressure, mmHg	86 (7)	90 (8)	88 (7)	0.11
Pulse pressure, mmHg	60 (13)	66 (16)	64 (16)	0.31
Total cholesterol, mmol/l	5.17 (1.14)	5.24 (0.87)	5.30 (0.69)	0.90
LDL cholesterol, mmol/l	3.10 (0.93)	3.02 (0.88)	3.22 (0.53)	0.41
HDL cholesterol, mmol/l	1.47 (0.32)	1.64 (0.45)	1.46 (0.30)	0.035
Triglycerides, mmol/l	1.36 (0.54)	1.26 (0.62)	1.43 (0.59)	0.45
hsCRP, mmol/l	3.04 (2.31)	3.07 (4.04)	2.20 (2.38)	0.56
LTPA				0.003
Low (randomly/never), n (%)	7 (39)	8 (10)	0 (0)	
Moderate (1-3 times/week), n (%)	6 (33)	45 (58)	12 (49)	
High (≥4 times/week), n (%)	5 (28)	24 (31)	13 (51)	
New diabetes, n (%)	2 (11.1)	7 (8.6)	1 (4.0)	0.66

Data is presented as mean (SD) except where indicated. ABI, ankle-brachial index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; LTPA, leisure-time physical activity; hsCRP, high-sensitivity C-reactive protein. Incident PAD = ABI ≤ 0.90; Stable ABI = ABI change < 0.15; Increased ABI = ABI change ≥ 0.15

(Study I: Heikkilä A, et al. Ann Vasc Surg. 2016 Apr; 32:50-6.)

The only independent factor which associated with an increase in ABI during the follow-up was LTPA in the multivariate analyses. High [(OR) 7.76 (95% CI: 2.39 – 25.20)] or moderate LTPA [(OR) 6.15 (95% CI: 1.99 – 19.1)] predicted rise in ABI groups in comparison to low LTPA (Table 3). In addition, there was no statistical difference among the three ABI groups in the usage of antihypertensive or lipid lowering drugs at baseline or at the follow-up visit.

Table 3. Multivariate ordered* logistic regression analyses relating baseline cardiovascular risk factors and LTPA to increase in ABI at follow-up

Cardiovascular risk factors	OR** (95% CI)	p
Change		
Systolic blood pressure /SD	0.86 (0.59 to 1.25)	0.43
Diastolic blood pressure /SD	1.03 (0.69 to 1.55)	0.87
Pulse pressure /SD	0.80 (0.55 to 1.16)	0.24
Body mass index /SD	0.78 (0.54 to 1.14)	0.20
LDL cholesterol /SD	1.01 (0.69 to 1.48)	0.96
Fasting glucose /SD	0.74 (0.50 to 1.09)	0.13
LTPA		<0.001***
Low (randomly/never)	1.00 (reference)	
Moderate (1-3 times/week)	6.15 (1.99 to 19.10)	
High (≥4 times/week)	7.76 (2.39 to 25.20)	
Smoking	0.73 (0.26 to 2.05)	0.56

*LDL, low-density lipoprotein; LTPA, leisure-time physical activity; SD, standard deviation; LDL, low-density lipoprotein. * code: 0 = Incident PAD, 1 = Stable ABI, 2 = Increased ABI; ** adjusted by sex, age and baseline ABI; *** p for linearity. (Study I: Heikkilä A, et al. Ann Vasc Surg. 2016 Apr; 32:50-6.)*

At baseline, 24 subjects were current smokers and during the 7-year follow-up, six (25 %) of them stopped smoking. Of these six, ABI increased in four and two developed incident PAD. Of all the study subjects, only five (4%) gave a positive response to the Edinburgh Claudication Questionnaire although they had no significant ABI change during the follow-up.

Ten (8%) subjects were diagnosed as diabetics during the follow-up, seven of them in the stable ABI group, two in the incident PAD group and one in the increased ABI group. Six subjects past away during the follow-up. The death rate per 1000 person-years was 7.3 (95% CI: 2.7 – 15.9).

5.2. Relationship between height and peripheral arterial disease (II)

The second study cohort after excluding subjects with intermittent claudication, previously diagnosed diabetes, cardiovascular or renal disease included 972 subjects with 517 (53%) women. The mean age for men and women were 58.1 ± 6.7 years and 58.8 ± 6.9 years, and the mean height 177 ± 7 centimeters and 163 ± 6 centimeters, respectively. The mean ABI for men was 1.09 ± 0.12 and for women 1.08 ± 0.12. The prevalence of PAD in both genders was 5% (95% CI 3-7%).

Characteristics of the study subjects are presented in the Tables 4 and 5 according to gender and quartiles of height. In both genders, there was an inverse relationship between height and age, pulse pressure and use of vasodilator drugs. Among men, taller height was associated with larger waist circumference. In addition, women in the shortest quartile of height had the highest BMI values.

Table 4. Characteristics of the male study subjects by quartiles of height

Characteristic, Men	Q1 (n=113)	Q2 (n=113)	Q3 (n=115)	Q4 (n=114)	p
Clinical					
Height, cm, mean (range)	168 (≤172)	174 (173-175)	179 (176-181)	185 (≥182)	
Age, y	61 (6)	58 (6)	57 (7)	56 (7)	<0.001[a]
Waist, cm	99 (11)	102 (10)	102 (12)	104 (10)	<0.001[a]
Body mass index, kg/m²	28.6 (4.1)	29.4 (4.4)	28.5 (4.4)	28.4 (3.7)	0.42[a]
SBP, mmHg	150 (18)	150 (16)	148 (17)	146 (19)	0.14[a]
DBP, mmHg	88 (9)	90 (8)	90 (8)	91 (10)	0.068[a]
Pulse pressure, mmHg	61 (14)	59 (13)	58 (14)	56 (13)	0.002[a]
Total cholesterol, mmol/l	5.14 (0.89)	5.25 (0.95)	5.30 (0.97)	5.25 (0.90)	0.32[a]
LDL cholesterol, mmol/l	1.40 (0.40)	1.44 (0.36)	1.40 (0.38)	1.33 (0.44)	0.11[a]
HDL cholesterol, mmol/l	3.09 (0.78)	3.16 (0.85)	3.26 (0.83)	3.23 (0.83)	0.12[a]
Triglycerides, mmol/l	1.41 (0.69)	1.46 (0.80)	1.45 (0.71)	1.54 (0.79)	0.21[a]
MetS, n (%)	40 (35)	49 (43)	49 (43)	55 (48)	0.069[a]
Glucose homeostasis, n (%)					0.21[b]
Normal	53 (47)	51 (45)	49 (43)	57 (50)	
IGT	32 (28)	33 (29)	41 (36)	43 (38)	
IFG	21 (19)	18 (16)	20 (17)	11 (10)	
Type 2 diabetes	7 (6)	11 (10)	5 (4)	3 (3)	
Health behaviors					
Current smokers, n (%)	25 (22)	29 (26)	25 (22)	30 (26)	0.63[a]
AUDIT	7.6 (5.8)	7.8 (6.4)	8.1 (5.7)	6.6 (5.1)	0.30[a]
LTPA, n (%)					0.25[b]
Low	11 (10)	9 (8)	11 (10)	10 (9)	
Moderate	66 (58)	71 (63)	84 (73)	77 (68)	
High	36 (32)	33 (29)	20 (17)	27 (24)	
Current medication, n (%)					
Vasodilatators	40 (35)	40 (35)	31 (27)	27 (24)	0.024[a]
Beta-blockers	29 (26)	22 (19)	16 (14)	22 (19)	0.14[a]
Diuretics	13 (12)	12 (11)	7 (6)	12 (11)	0.55[a]
Statins	19 (17)	15 (13)	14 (12)	12 (11)	0.16[a]

Data are presented as mean (SD) except where indicated. SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; IFG, Impaired fasting plasma glucose; LTPA, leisure-time physical activity; MetS, metabolic syndrome; AUDIT, Alcohol Use Disorders Identification Test.

p for linearity; [a] Linearity across quartiles of height; [b] differences between quartiles of height

(Study II: Heikkilä A, et al. Vasa. 2016 Nov;45(6):486-490.)

Table 5. Characteristics of the female study subjects by quartiles of height

Characteristic, Female	Q1 (n=129)	Q2 (n=129)	Q3 (n=129)	Q4 (n=130)	p
Clinical					
Height, cm, mean (range)	154 (≤132)	160 (158-161)	164 (162-166)	170 (≥167)	
Age, y	61 (7)	59 (7)	58 (7)	57 (7)	<0.001[a]
Waist, cm	94 (14)	93 (11)	94 (13)	96 (13)	0.11[a]
Body mass index, kg/m²	31.3 (6.9)	29.6 (4.9)	29.4 (5.3)	29.5 (5.3)	0.011[a]
SBP, mmHg	151 (17)	149 (18)	150 (19)	147 (18)	0.12[a]
DBP, mmHg	88 (7)	88 (8)	89 (9)	88 (8)	0.56[a]
Pulse pressure, mmHg	63 (15)	61 (14)	61 (14)	58 (14)	0.024[a]
Total cholesterol, mmol/l	5.39 (0.91)	4.43 (1.06)	5.36 (0.93)	5.28 (0.90)	0.27[a]
LDL cholesterol, mmol/l	1.63 (0.42)	1.57 (0.40)	1.52 (0.36)	1.54 (0.39)	0.045[a]
HDL cholesterol, mmol/l	3.18 (0.86)	3.23 (0.97)	3.25 (0.83)	3.15 (0.82)	0.81[a]
Triglycerides, mmol/l	1.30 (0.52)	1.39 (0.67)	1.31 (0.58)	1.37 (0.67)	0.59[a]
MetS, n (%)	57 (44)	70 (54)	52 (48)	66 (51)	0.49[a]
Glucose homeostasis, n (%)					0.072[b]
Normal	64 (50)	72 (56)	61 (47)	68 (52)	
IGT	55 (17)	27 (21)	35 (27)	40 (31)	
IFG	33 (26)	20 (16)	26 (20)	17 (13)	
Type 2 diabetes	10 (8)	10 (8)	7 (5)	5 (4)	
Health behaviors					
Current smokers, n (%)	11 (9)	18 (14)	17 (13)	15 (12)	0.52[a]
AUDIT	2.5 (2.8)	3.0 (3.9)	2.6 (2.5)	2.8 (2.9)	0.49[a]
LTPA, n (%)					0.56[b]
Low	25 (19)	26 (20)	15 (12)	25 (19)	
Moderate	87 (67)	88 (68)	93 (72)	88 (68)	
High	17 (13)	15 (12)	21 (16)	17 (13)	
Current medication, n (%)					
Vasodilatators	48 (37)	36 (28)	34 (26)	31 (24)	0.021[a]
Beta-blockers	26 (20)	37 (29)	26 (20)	27 (21)	0.68[a]
Diuretics	20 (16)	14 (11)	8 (6)	14 (11)	0.12[a]
Statins	18 (14)	31 (24)	14 (11)	17 (13)	0.27[a]

Data are presented as mean (SD) except where indicated. SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; IFG, Impaired fasting plasma glucose; LTPA, leisure-time physical activity; MetS, metabolic syndrome; AUDIT, Alcohol Use Disorders Identification Test.

p for linearity; [a] Linearity across quartiles of height; [b] differences between quartiles of height

(Study II: Heikkilä A, et al. Vasa. 2016 Nov;45(6):486-490.)

A positive association between height and ABI values ($p < 0.001$), was observed among men. Furthermore, in men, height was inversely associated with the prevalence of PAD ($p < 0.001$). After adjustment for age, waist circumference, pulse pressure, current smoking, glucose disorder and use of medication and LTPA, the association remained for ABI ($p = 0.011$) and for the prevalence of PAD ($p = 0.005$) (Figure 8). In women, these relationships did not exist (Figure 9).

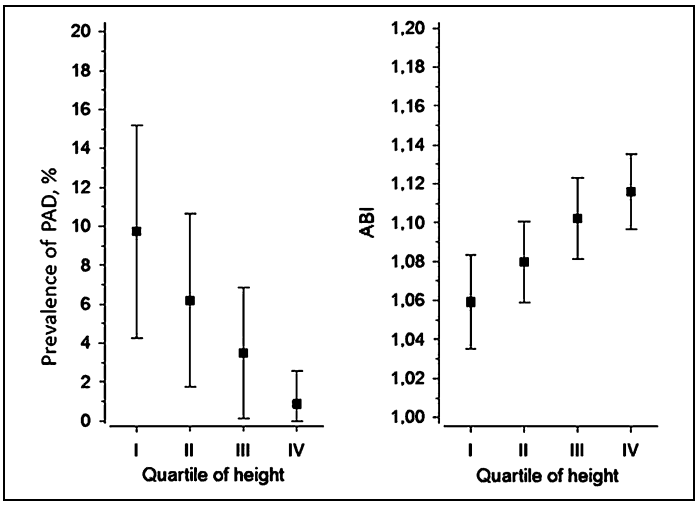

Figure 8. *Prevalence of PAD and mean ABI according to quartiles of height in men. Whiskers show 95% CIs. Adjusted for age, waist circumference, pulse pressure, current smoking, glucose disorder and use of medication and LTPA. (Study II: Heikkilä A, et al. Vasa. 2016 Nov;45(6):486-490.)*

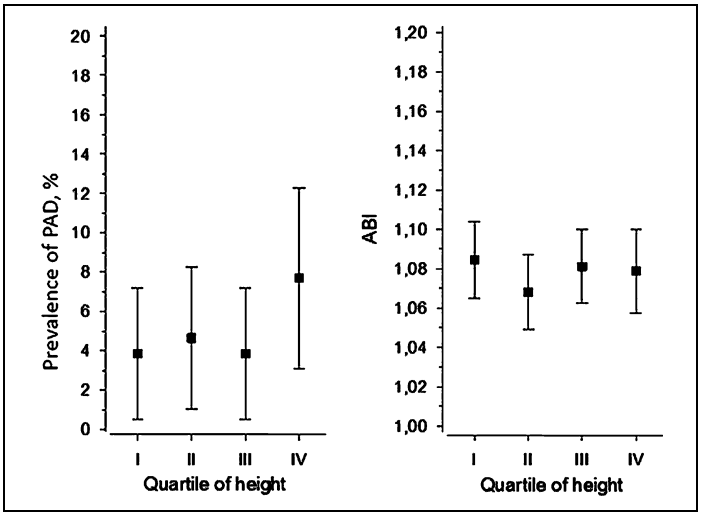

Figure 9. *Prevalence of PAD and mean ABI according to quartiles of height in women. Whiskers show 95% CIs. Adjusted for age, waist circumference, pulse pressure, current smoking, glucose disorder and use of medication and LTPA. (Study II: Heikkilä A, et al. Vasa. 2016 Nov;45(6):486-490.)*

After performing the multivariate logistic regression analyses the association between quartiles of height and PAD remained in men (p = 0.029). Moreover, a significant correlation between PAD and current smoking as well as age was observed among men. In women, only pulse pressure was associated with PAD (Table 6).

Table 6. Multivariate logistic regression analyses of factors associated with PAD by gender

	Men		Women	
Variable	OR (95% CI)	p	OR (95% CI)	p
Quartiles of height		0.029*		0.14*
I	1.00 (Reference)		1.00 (Reference)	
II	0.78 (0.27 to 2.21)		1.26 (0.35 to 4.61)	
III	0.51 (0.15 to 1.77)		1.08 (0.28 to 4.09)	
IV	0.10 (0.01 to 0.87)		2.81 (0.83 to 9.52)	
Age	1.13 (1.04 to 1.22)	0.004	0.99 (0.91 to 1.06)	0.69
Waist	1.02 (1.03 to 1.22)	0.27	1.03 (0.99 to 1.06)	0.091
Pulse pressure	1.02 (0.98 to 1.05)	0.33	1.08 (1.05 to 1.11)	<0.001
Fasting glucose	0.76 (0.45 to 1.27)	0.30	1.06 (0.72 to 1.56)	0.77
Total cholesterol	0.92 (0.57 to 1.49)	0.75	1.24 (0.79 to 1.94)	0.36
Current smoking	4.26 (1.66 to 10.94)	0.003	1.82 (0.58 to 5.74)	0.31

**p for linearity. (Study II: Heikkilä A, et al. Vasa. 2016 Nov;45(6):486-490.)*

5.3. Peripheral arterial disease and erectile dysfunction (III)

The study group included 380 men (mean age 56.9 ± 6.5 years) after excluding subjects with previously diagnosed cancer or neurological disease (Parkinson´s disease, multiple sclerosis) and female subjects. Among these men the mean ABI was 1.09 ± 0.11 and the prevalence of PAD and borderline ABI was 4% (95% CI 2-6%) and 17% (95% CI 13-20%), respectively. Men with moderate or severe ED (17%) had a mean ABI of 1.06 ± 0.12.

Characteristics of the study subjects according to ED are shown in Table 7. Men with ED were older, less educated, had more often depressive symptoms than men without ED. Their ABI values were also lower compared to men without ED (p = 0.005). The cumulative distribution of ABI in individuals with and without ED is illustrated in Figure 10. There were no significant associations between ED and other cardiovascular risk factors such as smoking, lipid metabolism or glucose.

Table 7. Characteristics of the subjects according to the presence of erectile dysfunction

	No erectile dysfunction n = 315	Erectile dysfunction n = 65	p
Demographic			
Age, years	56 (6)	61 (6)	<0.001
BMI, kg/m^2	29.0 (4.3)	27.9 (2.9)	0.12
WC, cm	101.6 (10.8)	99.5 (8.5)	0.27
Cohabiting, n (%)	265 (89)	52 (85)	0.46
Education, n (%)			0.002
primary	204 (68)	55 (90)	
secondary	59 (20)	5 (8)	
high school	37 (12)	1 (2)	
Clinical			
SBP, mmHg	142 (18)	144 (16)	0.50
DBP, mmHg	89 (10)	89 (11)	0.83
PP, mmHg	54 (14)	55 (14)	0.48
TC, mmol/l	5.37 (0.95)	5.30 (0.95)	0.62
HDL-C, mmol/l	1.40 (0.38)	1.44 (0.37)	0.37
LDL-C, mmol/l	3.28 (0.86)	3.20 (0.89)	0.46
TG, mmol/l	1.53 (0.74)	1.49 (0.83)	0.78
Glucose, mmol/l	5.71 (0.99)	5.81 (0.68)	0.42
BDI	4.4 (4.2)	7.8 (5.5)	<0.001
BDI ≥10, n (%)	39 (13)	18 (29)	<0.001
ABI	1.10 (0.11)	1.06 (0.12)	0.005
ABI-category, n (%)			0.005
normal ABI	260 (83)	42 (65)	
borderline ABI	45 (14)	18 (28)	
incident PAD	10 (3)	5 (8)	
Lifestyle factors			
Current smokers, n (%)	89 (28)	16 (25)	0.55
AUDIT score	7 (6)	9 (7)	0.27
LTPA, n (%)			0.25
low	223 (72)	40 (62)	
moderate	53 (17)	16 (25)	
high	35 (11)	9 (14)	

Data are presented as mean (SD) except where indicated. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; BDI, Beck's Depression Inventory; AUDIT, Alcohol Use Disorders Identification Test; LTPA, leisure-time physical activity. Normal ABI = 1.01-1.40; borderline ABI = 0.91-1.00; incident PAD = ABI ≤ 0.90

Figure 11 illustrates the effect of age and ABI on ED. After the age of 60, odds ratios for ED increased significantly per 1-SD decrease of ABI. The model was adjusted for the score of depressive symptoms, cohabiting status, LDL-C, fasting plasma glucose, pulse pressure, BMI, and smoking.

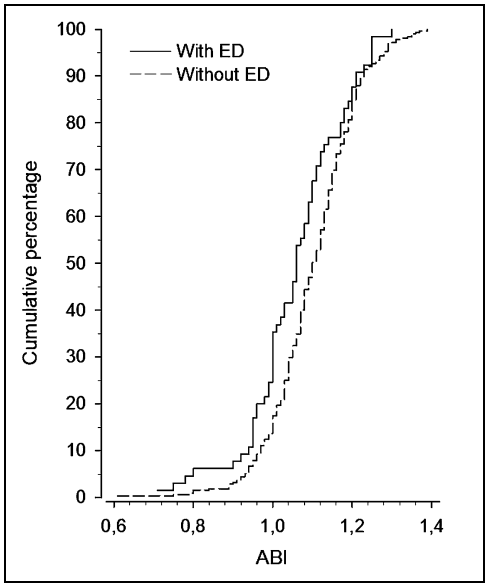

Figure 10. *The cumulative distribution of ABI in individuals with and without ED.*

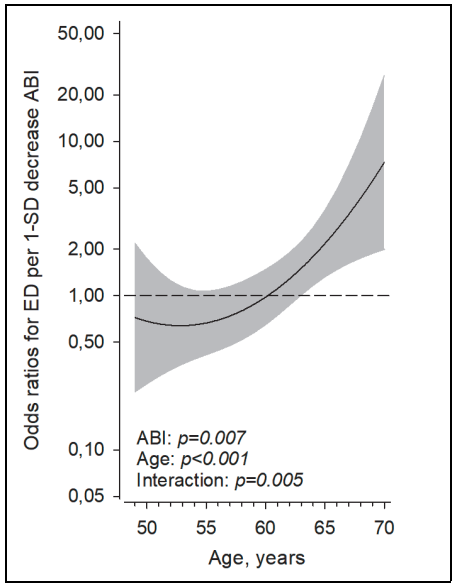

Figure 11. *Effects of age and ABI for ED. Model including quadratic terms for age. Gray area shows 95 per cent confidence limits. Adjusted for the score of depressive symptoms, cohabiting status, LDL-C, fasting plasma glucose, pulse pressure, BMI, and smoking.*

5.4. The relationship of blood pressure and erectile dysfunction (IV)

Among 665 men (mean age 56 ± 6 years) with at least one cardiovascular risk factor but without manifested chronic diseases or medication affecting vasculature, 52% had ED according to the IIEF-5 questionnaire. Table 8 demonstrates the characteristics and health behaviours of the subjects.

Men with normal erectile function were younger, more often cohabiting and better educated than men with ED. They also suffered less from depressive symptoms and had lower SBP and PP levels compared to men with ED.

Table 8. Characteristics of the subjects according to the presence of erectile dysfunction

	No erectile dysfunction n = 320	Erectile dysfunction n = 345	p
Demographic			
Age, years	54 (6)	58 (6)	<0.001
Cohabiting, n (%)	278 (89)	282 (83)	0.028
Education, n (%)			<0.001
primary	187 (60)	257 (76)	
secondary	74 (24)	51 (15)	
high school	50 (16)	29 (7)	
BMI, kg/m^2	27.8 (3.7)	27.6 (3.7)	0.37
WC, cm	98.8 (9.4)	98.9 (10.2)	0.57
Clinical			
SBP, mmHg	138 (19)	141 (19)	0.054
DBP, mmHg	86 (9)	86 (11)	0.81
PP, mmHg	52 (15)	55 (14)	0.021
TC, mmol/l	5.29 (0.92)	5.39 (0.98)	0.21
HDL-C, mmol/l	1.43 (0.37)	1.41 (0.36)	0.45
LDL-C, mmol/l	3.25 (0.82)	3.34 (0.87)	0.21
TG, mmol/l	1.37 (0.72)	1.44 (0.79)	0.20
Glucose, mmol/l	5.55 (0.72)	5.67 (1.09)	0.11
Metabolic syndrome, n	88 (28)	101 (31)	0.41
(%)	3.5 (3.8)	5.7 (5.1)	<0.001
BDI	27 (9)	64 (19)	<0.001
BDI ≥10, n (%)			
Lifestyle factors	66 (21)	87 (25)	0.16
Current smokers, n (%)	7 (5)	7 (6)	0.70
AUDIT score			0.052
LTPA, n (%)	241 (76)	236 (69)	
low	51 (16)	58 (17)	
moderate	25 (8)	46 (14)	
high			

Data are presented as mean (SD) except where indicated. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; BDI, Beck's Depression Inventory; AUDIT, Alcohol Use Disorders Identification Test; LTPA, leisure-time physical activity.
(Study IV: Heikkilä A, et al. J Sex Med. 2017 Nov;14(11):1336-1341.)

After adjustment for age, fasting plasma glucose, waist circumference, cohabiting status, education, and the prevalence of depressive symptoms, the curve correlating DBP values and the prevalence of ED was U-shaped with a nadir of DBP 90 mmHg. Conversely, the effect of PP values on the prevalence of ED was inversely U-shaped. When the reference level was set at PP 60 mmHg, lower and higher PP values were associated with lower prevalence of ED (Figure 12).

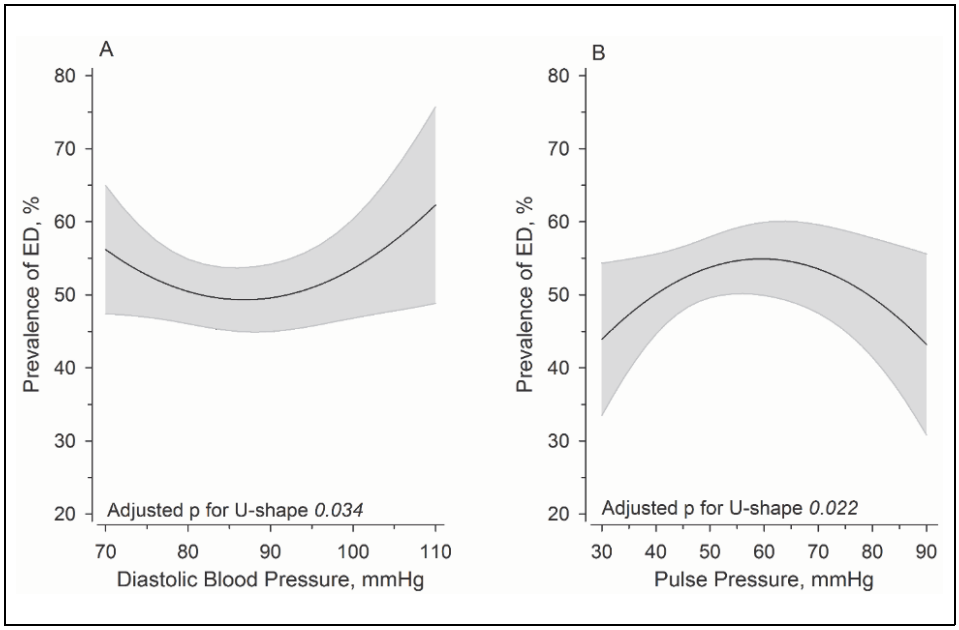

Figure 12. *Effect of diastolic blood pressure level (A) and pulse pressure level (B) on the prevalence of erectile dysfunction. The 95 per cent confidence intervals are denoted by gray areas. Adjusted for age, cohabiting status, education, fasting plasma glucose, waist circumference, and the prevalence of depressive symptoms.*
(Study IV: Heikkilä A, et al. J Sex Med. 2017 Nov;14(11):1336-1341.)

6. DISCUSSION

6.1. Study population

In this thesis we investigated a well-defined cardiovascular risk population derived from the Harmonica project, a population-based survey. With a reasonably high participation rate of 74% the inhabitants from two the rural towns of Harjavalta and Kokemäki took part in this survey in a primary care setting. The main focus of this thesis was PAD and therefore we concentrated on the participants from Harjavalta who had their ABI measured. ABI measurement was not performed on participants from Kokemäki. However, in study IV, we included all the men from Harjavalta and Kokemäki in the analysis because of the special focus on ED.

Subjects with intermittent claudication, previously diagnosed diabetes, cardiovascular or renal disease were excluded to ensure a more homogenous and comorbid-free cohort of individuals from the general population to evaluate the associations between PAD and cardiovascular risk factors. Due to the cross-sectional nature of studies II-IV, no causalities can be evaluated from these associations. However, a prospective study design was used in the first study, with an average follow-up time of seven years. Although, the number of followed borderline ABI subjects was quite low (n=123) with a participation rate of 65%, the follow-up time was reasonably long and the study population was well-defined. Still, this small sample size lowers the statistical power to detect effect sizes in this longitudinal study.

6.2. Methods

Ankle-Brachial Index

ABI was measured by a single physician at baseline and a trained nurse at the follow-up. As the recent American Heart Association statement suggests, we calculated ABI using the lower ankle SBP of the left and right leg in order to find a higher number of persons with increased risk for future cardiovascular events (Aboyans et al. 2012). The measurement of the ankle SBP was performed from both legs but for logistic reasons we used primarily the ADP pulsation. The ATP pulsation was only used if the pulsation from the ADP was not detected. There is the possibility that in some subjects the ABI values could have been higher if SBP from ATP had been used for measuring ABI. Thus, the American Heart Association statement for ABI measurement recommends using the higher ankle SBP from ADP and ATP for each leg (Aboyans et al. 2012). Therefore, the

prevalence of PAD may be overestimated in our study. In addition, the ABI measurement was performed with a validated Doppler instrument and appropriate-sized blood pressure cuffs were used (Aboyans et al. 2012).

Erectile dysfunction

The IIEF-5, a questionnaire we used to test for presence and severity of ED, has a limitation regarding its inability to evaluate erectile function in sexually inactive men (Yule et al. 2011). Men reporting sexual inactivity over the past six months could have been comprised respondents who may have an adequate erection, but do not have a partner or do not have sexual contact with their partner. In studies III and IV, we excluded all men reporting a zero score in any of the IIEF-5 questions. This removal of the zero category for men who were not sexually active over the past six months, may increase the accuracy in prevalence estimates of ED or vice versa lead to a selection bias.

For large-scale epidemiological studies it is more practical to screen erectile function using valid self-reported outcome measures such as the widely used IIEF-5 questionnaire, which is also cross-culturally validated in the Finnish language. As a comparison, the duplex doppler ultrasound would give a more objective and recall-free assessment of the erectile function. However, it would also be a more expensive and more time-consuming instrument, and thus not so suitable for a primary care setting. Moreover, the absence of a validated questionnaire for lower urinary track symptoms, a well-defined risk factor for ED (Blanker et al. 2001), can be considered as a weakness of the study.

The lack of medical history for ED in our study population can be regarded as a limitation. Although no data were available on the usage of phosphodiesterase type 5 inhibitors (PDE5I) by our study subjects, we estimated the consumption to be quite low, because at the time our study was conducted, sildenafil was the only PDE5I on the market and the price per tablet was quite high. The usage of such medications would probably result in men reporting a better erectile function rather than a poor one, thus underestimating the prevalence of ED.

Blood pressure

Blood pressure measurements were obtained by trained medical staff during the office visit according to the guidelines of the European Society of Hypertension (Parati et al. 2008). The same recommendations were followed when subjects were taught to perform BP monitoring at home.

Anthropometric measurements

The anthropological measurements used in the Harmonica Project were performed according to the WHO Monica standards (WHO MONICA Project 1988). Height and weight were measured with the subject in a standing position without shoes or outer garments by a trained nurse. The mean heights for both women and men in study II were equal to the mean heights of Finns in 2007, i.e., 163cm in women and 177cm in men (Peltonen et al. 2007).

6.3. Physical activity and peripheral arterial disease (I)

We demonstrated in our prospective study-arm that physical activity significantly associates with improved ABI values among both genders with borderline ABI. High and even moderate LTPA was found to predict a rise in ABI compared to low LTPA.

Traditionally, exercise is a beneficial and recommended treatment for patient with symptomatic PAD (McDermott et al. 2009). Also among asymptomatic PAD patients, higher levels of exercise are known to associate with lower odds of PAD defined by ABI < 0.9 (R. A. Stein et al. 2015). Recently, patients with borderline ABI have been recognized to have increased risk of CVD events and mortality. In 2008, the Ankle Brachial Index Collaboration published a large-scale meta-analysis including 16 cohort studies, with participants from the general population aged 47-78 years without a history of CAD (Ankle Brachial Index Collaboration et al. 2008). In men with borderline ABI 0.91–1.00, the hazard ratios for total mortality, cardiovascular mortality and major coronary events were 1.61, 1.68 and 1.43, respectively, when compared to reference subjects (ABI 1.11–1.20) (Ankle Brachial Index Collaboration et al. 2008). The corresponding ratios in women were 1.52, 1.84 and 1.53 (Ankle Brachial Index Collaboration et al. 2008). These results inspired us to investigate the progression of PAD with ABI measurement in borderline ABI patients without previously diagnosed diabetes, cardiovascular disease, renal disease or intermittent claudication.

Our results appear to be similar as those of several prior large-scale observational studies that have assessed the relationship between physical activity and ABI values. A robust cross-sectional nationwide study with over three million US participants from 2003 to 2008 demonstrated that subjects who reported any physical activity had significantly lower odds of PAD (OR 0.64) even after adjustment for multiple cardiovascular risk factors (R. A. Stein et al. 2015). PAD was defined by ABI<0.9 in either leg (R. A. Stein et al. 2015). Higher frequency of physical activity was also associated with lower prevalence of PAD in a graded manner (R. A. Stein et al. 2015). In addition, subjects with intermittent claudication, angina, and lower extremity neuropathy, were excluded from the

analyses (R. A. Stein et al. 2015). The Cardiovascular Health Study demonstrated with an elderly population (>65 years-old) an inverse relation between exercise intensity and the prevalence of a low ABI (<0.9) (Siscovick et al. 1997). Another cross-sectional study by Bertoni et al reported from the Multi-Ethnic Study of Atherosclerosis that moderate-to-vigorous and intentional exercise associates with higher ABI values (Bertoni et al. 2009). Moreover, in line with our study, a recent prospective study also derived from the Multi-Ethnic Study of Atherosclerosis, with participants free of clinically evident CVD and baseline ABI between 0.90 to 1.40, stated that participation in intentional exercise protects against incident PAD (ABI ≤ 0.90) (Delaney et al. 2013). Another longitudinal study conducted in Malmö, Sweden, found this protective effect of physical activity to reduce the occurrence of asymptomatic leg atherosclerosis even in men who had begun to exercise after the age of 55 years (Engstrom et al. 2001). In this study, the follow-up time was 13 years and asymptomatic PAD was assessed using calf plethysmography at baseline and ABI measurement (<0.90) at follow-up (Engstrom et al. 2001). Even among patients with type 2 diabetes exercise training may delay the progression of PAD according to ABI measurement (Barone Gibbs et al. 2013). In this randomized trial, using a six-month supervised exercise program, Barone et al demonstrated with 114 diabetics that ABI increased in exercisers compared to controls, and that the increase was stronger in patients with lower baseline ABI values (ABI < 1.0) (Barone Gibbs et al. 2013). In addition, increased ABI correlated with better glucose values and BP levels although the change in ABI values was independent of these associations (Barone Gibbs et al. 2013). The participants in our study received multifactorial recommendations for lifestyle modification without any further supervision, which is a manageable demand in a primary care setting.

Traditional risk factors for PAD, such as high BP or glucose values, smoking and dyslipidemia, did not associate with increased ABI values in our study population. This may be due to the small sample size that lowers the statistical power to detect these effects or the fact that our study cohort had a moderate overall risk factor burden at baseline, after excluding subjects with previously diagnosed diabetes, cardiovascular or renal disease. Medications for hypertension and dyslipidemia were used evenly between the ABI groups. It is also a known fact, that LTPA has a positive impact on weight loss, blood pressure and cholesterol values (Cornelissen & Smart 2013, Thorogood et al. 2011, Cornelissen et al. 2013, Kodama et al. 2007). These associations may have influenced the positive correlation between LTPA and increased ABI values in our study.

Over the years, ABI values tend to decline as PAD progresses. A prospective study among subjects with and without intermittent claudication derived from the Edinburgh Artery Study was conducted in Scotland from 1988 to 2000 (F. B. Smith et al. 2003). Changes in ABI for each leg was recorded, at baseline in 1988

and at subsequent five-year and 12-year follow-up (F. B. Smith et al. 2003). Among asymptomatic subjects the overall ABI decrease was 0.025 over five years (F. B. Smith et al. 2003). The decline was more rapid in the leg with the higher ABI at baseline (F. B. Smith et al. 2003). Moreover, ABI declined more in both legs among subjects with intermittent claudication compared to subjects without intermittent claudication (F. B. Smith et al. 2003). Conversely, in our asymptomatic study population the mean ABI values improved significantly during the seven-year follow-up time. We assume that our multifactorial intervention was the main reason behind this outcome.

6.4. The relationship between height and peripheral arterial disease (II)

In this study, we demonstrated an inverse association between height and the prevalence of PAD (ABI $\leq$ 0.90) among men without previously diagnosed cardiovascular or renal disease or diabetes. Furthermore, height in men was negatively associated with ABI values even after adjustment for traditional cardiovascular risk factors. These associations were not significant among women.

The evidence is weak regarding the relationship between body height and PAD. The link between height and CAD is clearer and more often studied (Paajanen et al. 2010). Two observational studies with diabetic patients have reported a direct correlation between height and ABI (Hiatt et al. 1995, Fu et al. 2015). A low-risk subset of a study population derived from the San Luis Valley Diabetes Study was investigated to assess the diagnostic criteria of PAD by Hiatt et al (Hiatt et al. 1995). They found a moderate association between height and ankle pressure after adjusting for arm pressure, sex, diabetes status and age (Hiatt et al. 1995). For each 10 cm in height, there was an approximate 1 mm Hg increase in ankle pressure (Hiatt et al. 1995). A more recent and focused study regarding the association between height and PAD was conducted in China (Fu et al. 2015). With over 4500 patients with type 2 diabetes Fu et al demonstrated that men and women in the shortest stature group had 1.174 and 1.143 times greater risk of PAD, respectively, compared to those in the tallest stature group (Fu et al. 2015). In the multivariate model hazard ratio for PAD for a 10-cm height increase was 0.85 (Fu et al. 2015). However, ABI values might be falsely higher in diabetic patients due to arterial calcification and the number of PAD patients could be underestimated. In our study, subjects with previously diagnosed diabetes were excluded to minimize this possible bias.

In our analysis, we were able to demonstrate the association between height and PAD only in men. Similar results in other vascular beds have been reported (Rosenberg et al. 2014, Nelson et al. 2015). Nelson et al using genetic variants

confirmed the inverse association between height and risk of CAD in men (OR 0.88) but not in women (Nelson et al. 2015). In detail, only men had a relative increase of 13.5% in the risk of coronary heart disease for each SD decrease in genetically determined height (Nelson et al. 2015). Moreover, previous studies have proposed that the gender difference in ABI values might be explained partially by height (Fowkes et al. 1991). Among women in our study pulse pressure was associated with PAD, which may have been explained by the higher levels of pulse pressure found in women compared to men.

The role of human height in vascular diseases is revealing. More studies with larger populations should be conducted to confirm the association between height and PAD. In the future, prospective studies could help us to discover how human height influences the natural progression of PAD and whether the clinical manifestations of PAD associate with height. Although height is determined mainly by genetic factors it could serve as a potential risk factor for PAD.

6.5. Erectile dysfunction and peripheral arterial disease (III)

Among elderly men, moderate to severe ED was associated with lower ABI values in a cardiovascular risk population. In these apparently healthy men, after the age of 60 years, odds ratios for ED increased significantly per 1-SD decrease of ABI, even after adjusting for confounding factors.

There are few studies regarding the association between ED and PAD (Polonsky et al. 2009, Chai et al. 2009, Lahoz et al. 2016, D. I. Feldman et al. 2016, Banks et al. 2013). The results of these studies are diverse. A large prospective study among Australian men without previously diagnosed CVD found a correlation between severity of ED and PAD (Banks et al. 2013). Men with severe ED had an almost two times greater risk for PAD compared to men with no ED (Banks et al. 2013). PAD was defined from database diagnoses and ED with a single self-assessment question (Banks et al. 2013). In a retrospective insurance database study, Blumentals et al reported that men with ED had a 75% increase in risk for PAD than men without ED (Blumentals et al. 2003). Their results also suggested a trend towards increased risk in elderly men (Blumentals et al. 2003). Compared to men aged 30-39 years, it was reported that men aged 45-49 and 50-55 years were 2.3 and 3 times more likely to develop PAD, respectively (Blumentals et al. 2003). This age dependent trend corroborates our results. In addition, in the Rancho Bernardo Study, Chai et al evaluated 185 community-dwelling men, average age 71 years, and reported a significant association between low toe-brachial index and the severity of ED, defined by the IIEF-5 questionnaire (Chai et al. 2009). They concluded that there is a diffuse microvascular process involving these small-vessel arterial beds (Chai et al. 2009). In a more selective study population of 623

men referred for cardiac stress testing, increasing severity of ED was associated with elevated risk of asymptomatic PAD, defined as ABI ≤ 0.90 (Polonsky et al. 2009). In this study, the authors also reported a gradual increase in the prevalence of PAD with increasing ED severity, 28% of men with mild ED, 33% with moderate ED, and 40% with severe ED (Polonsky et al. 2009).

Although some studies, as previously mentioned, have shown that ED is an independent risk factor for PAD, others have failed to confirm this association. Recently two studies have evaluated this association and published negative results (D. I. Feldman et al. 2016, Lahoz et al. 2016). Feldman et al studied the association between ED and subclinical measures of atherosclerosis; ABI (<0.9 or >1.4), carotid intima-media thickness, coronary artery calcium and carotid plaque score (D. I. Feldman et al. 2016). The study population was derived from the prospective Multi-Ethnic Study of Atherosclerosis, with 1862 men aged 45-84 years and free of known CVD (D. I. Feldman et al. 2016). Surprisingly, abnormal ABI was the only subclinical measure of vascular disease that lacked significant association with ED, as defined by a standardized, single direct question on ED symptoms (D. I. Feldman et al. 2016). In the fully adjusted models only coronary artery calcium and carotid plaque score remained statistically significant factors. The authors suggested that the variability caused by the measurement of ABI, might impact the accuracy of the test and be a biasing factor (D. I. Feldman et al. 2016). The second study was published in 2016 by Lahoz et al, including 614 randomly selected middle-aged Spanish men (Lahoz et al. 2016). Among these men, the presence of ED, defined by IIEF-5, was associated neither with the mean ABI nor the prevalence of men with ABI < 0.9 (Lahoz et al. 2016). However, a trend between a lower ABI and increasing ED severity was observed (Lahoz et al. 2016). In addition, another vascular domain, the carotid arteries, was found to associate with ED in their study (Lahoz et al. 2016). Men with ED had significantly higher carotid intima-media thickness and the prevalence of carotid plaques was more frequent (Lahoz et al. 2016).

At the moment there are no guidelines for screening PAD among men presenting with ED (Norgren et al. 2007, Aboyans et al. 2018). However, guidelines for ED highlight the association between ED and CVD including PAD (Hatzimouratidis et al. 2010). The current study implies that physicians should consider measuring ABI in elderly men suffering from ED. As there is a reasonably large amount of evidence regarding the relationship between ED and CVD, especially CAD, experts have proposed recommendations to add questions about ED to cardiovascular risk assessment tools, such as the Framingham Risk Score and the HEART SCORE (Jackson et al. 2013).

6.6. The relationship of blood pressure and erectile dysfunction (IV)

Among 665 men without previously diagnosed hypertension, cardiovascular diseases, renal disease or diabetes, we observed a U-shaped association between DBP values and the prevalence of ED. Moreover, the prevalence of ED increased

in men with higher or lower DBP values than 90mmHg. The effect of PP values on the prevalence of ED was reverse.

Although the link between essential hypertension and ED is generally confirmed (Burchardt et al. 2000, Javaroni & Neves 2012, Doumas & Douma 2006) , only few studies have investigated the association in detail. Similar to our finding, Kakkavas et al published a paper where they investigated ED in 174 men with untreated, newly diagnosed essential hypertension (Kakkavas et al. 2013). They observed with the IIEF-5 that both 24-hour ambulatory and office DBP were lower in the ED group, but not statistically significant (Kakkavas et al. 2013). In addition, U- and J-shaped relationships between DBP and cardiovascular morbidity and mortality have been demonstrated in several observational studies (Stewart 1979, Cruickshank 1988, Bangalore et al. 2010).Our results emphasize the role of DBP in ED, implying that DBP around 90 mmHg is optimal for erectile function. A possible explanation for this finding could be that significant changes in DBP may impair the complex hemodynamics of penile erection involving venous outflow occlusion within the corpora cavernosa and the DBP dependent perfusion pressure needed to maintain that occlusion.

Another interesting finding in this study was the association between PP and the prevalence of ED with an inverse U-shaped relation. Traditionally, arterial stiffness can be evaluated indirectly by measuring PP (Stehouwer et al. 2008). Moreover, PP is considered an independent predictor of CAD and cardiovascular mortality (Franklin et al. 1999, Benetos et al. 1997). However, our study population was considerably young and without any known atherosclerotic burden. It is worth noting that PP also depends on left ventricular ejection and the timing and intensity of reflected pressure waves from the periphery. It is possible that relatively high PP in men without arteriosclerosis reflects the pulsatile component of the blood pressure wave and increased penile blood flow. On the other hand, in subjects with low PP the elasticity of arteries may protect from ED.

Although it has been shown that smoking and low physical activity are associated with ED (Dorey 2001, Bacon et al. 2006), there are conflicting results regarding the relationship between LTPA and ED (J. He et al. 2007). In our study, smoking cessation or increased LTPA did not enhance erectile function. Clearly, lifestyle advice is still a logical method to treat and prevent ED, as well as concomitant cardiovascular risk factors including hypertension. Since 19% of the men with ED in our study also had depressive symptoms, screening for depression, a highly prevalent disorder in primary care, might be warranted among men suffering from ED.

Previous studies from Finland have reported quite high prevalence rates of ED (Shiri et al. 2003, Koskimaki et al. 2000). Shiri et al reported 77% prevalence of ED among men aged 50 to 75 years (Shiri et al. 2003) and Koskimaki et al 74%

(Koskimaki et al. 2000). In both studies ED was defined by two questions on the subject´s ability to achieve and maintain erection sufficient for intercourse (Shiri et al. 2003, Koskimaki et al. 2000). After taking into account that our study population was slightly younger and men with CVD and diabetes were excluded, these rates seem similar to ours. In addition, we used IIEF-5 for defining ED. In the Massachusetts Male Aging study Feldman et al. found that 52% of men aged 40–70 years had erectile dysfunction (H. A. Feldman et al. 1994). Furthermore, the age-adjusted prevalence of complete impotence was higher in patients with treated hypertension than in the entire cohort, 15% and 9.6%, respectively (H. A. Feldman et al. 1994). In hypertensive men, age, duration and severity of hypertension, depression, and antihypertensive medication have been associated with ED (Jensen et al. 1999, Grimm et al. 1997, Korhonen et al. 2015, F. A. Giuliano et al. 2004). Particularly thiazide diuretics and beta blockers have been shown to associate with ED in hypertensive men (Cordero et al. 2010, Grimm et al. 1997). Pathophysiological factors affecting penile erection such as endothelial dysfunction and smooth muscle cell damage might be induced by high blood pressure (Toblli et al. 2000, Clavijo et al. 2014, Jiang et al. 2005). In our study population, we observed an increase in ED prevalence when DBP dropped under 90mmHg which could partially explain the finding that blood pressure lowering agents, irrespective of class, may cause ED (Grimm et al. 1997). It is worth noting that none of our study subjects used antihypertensive medication.

7. CONCLUSIONS

On the basis of this study, the following conclusions can be drawn:

1. High physical activity may increase the borderline ABI values in long-term follow-up.
2. In men, height has a positive linear relationship with ABI values, and short stature is associated with higher prevalence of PAD. In women, these associations do not exist.
3. The presence of ED is associated with lower ABI values in men over 60 years of age without clinical manifestations of PAD.
4. The prevalence of ED and DBP values have a U-shaped association. It seems that DBP around 90 mmHg is optimal for erectile function.

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Arto Heikkilä

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