TIINA AHTI

Risk Factors of Varicose Veins

ACADEMIC DISSERTATION
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To my Family

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LIST OF ORIGINAL COMMUNICATIONS

This dissertation is based on the following original communications, referred to in the text by their Roman numerals, I–IV.

I Jukkola TM, Mäkivaara LA, Luukkaala T, Hakama M and Laurikka J (2006): The effects of parity, oral contraceptive use and hormone replacement therapy on the incidence of varicose veins. J Obstet Gynaecol 26:448–51.

II Ahti TM, Mäkivaara LA, Luukkaala T, Hakama M and Laurikka JO: Lifestyle factors and varicose veins – does cross-sectional design result in underestimate of the risk? Phlebology, in press.

III Ahti TM, Mäkivaara LA, Luukkaala T, Hakama M and Laurikka JO (2009): Effect of family history on the incidence of varicose veins: A population-based follow-up study in Finland. Angiology 60:487–91.

IV Ahti TM, Mäkivaara LA, Luukkaala T, Hakama M and Laurikka JO: Effect of family history on the risk of varicose veins is affected by differential misclassification. J Clin Epidemiol, in press. [Epub ahead of print 2010 Jan 5].

ABBREVIATIONS

BMI	body mass index
CEAP	clinical, etiologic, anatomic and pathophysiologic classification system for venous disease
CI	confidence interval
HRT	hormone replacement therapy
IOR	incidence odds ratio
OC	oral contraceptive pills
OR	odds ratio
VV	varicose veins

ABSTRACT

The aim of the study was to evaluate a range of potential risk factors in the etiology of varicose veins by a longitudinal follow-up study in a general middle-aged population. Studied factors were parity, use of oral contraceptives and hormone replacement therapy, lifestyle factors and self-reported family history of varicose veins. The purpose was also to evaluate misclassification in self-reported family history of varicose veins.

The five-year follow-up data was obtained through postal questionnaires from three cohorts of residents of the city of Tampere in Finland. The number of original target population of 40-, 50- and 60-year-olds was 6,874. The response rate was 81% (5,568) at entry. An almost identical questionnaire was sent five years later to those who had responded to the first questionnaire and the response rate was 88% (4,903). The questionnaire included questions related to medical conditions, lifestyle, varicose veins and family history of varicose veins. A sub-sample of subjects underwent a physical examination but family members were not clinically examined. Incidence of varicose veins was studied as an indicator of risk in those free of varicose veins at entry.

It was found that new varicose veins appeared more often in women with three or more births than in nulliparous women, incidence odds ratio, IOR 2.0 (95% confidence interval, CI: 1.0–3.9). Subjects who consumed alcohol weekly had a higher incidence of varicose veins compared to non-users, IOR 1.5 (95% CI: 1.05–2.3). The result was statistically significant only in women. Compared to non-smokers, subjects who had ever smoked for over a year, and of these heavier smokers (≥15 cigarettes a day), had higher risk of varicose veins, IORs 1.3 (95% CI: 0.9–1.8) and 1.8 (95% CI: 1.1–2.8) respectively. Daily use of meat seemed to decrease the risk of varicose veins compared to infrequent use (0–2 meals a week) of meat, particularly in women. Dietary fiber intake, use of contraceptive pills or hormone replacement therapy did not have an effect on the incidence of varicose veins.

In those with a positive family history of varicose veins the risk of varicose veins was increased compared to those with negative family history, IOR 1.6 (95% CI: 1.1–2.3). When genders were studied separately, the higher risk was statistically significant only in women, IOR 1.8 (95% CI: 1.1–2.8), but not in men, IOR 1.4 (95% CI: 0.7–2.6). The estimates of the risk were much lower than our prevalence results (OR 6.6 in men and OR 4.9 in women, respectively) and also those usually reported in the literature based on cross-sectional studies with prevalence estimates.

Subject's own varicose vein status or change in it was associated with self-reported family history of varicose veins. For example, if a person who at entry reported negative family history developed varicose veins during follow-up, the risk of reporting a family member with varicose veins after the follow-up was sixfold, OR 6.0 (95% CI: 2.0–47.8). If another person reported varicose veins at entry and at the end of the follow-up, the risk of reporting a new family member with varicose veins was less than 1 (OR 0.8 (95% CI: 0.6–0.9)).

In conclusion, in women, multiparity, alcohol consumption and positive family history of varicose veins increase the risk of varicose veins, whereas meals containing meat may reduce the risk. Smoking is likely a risk factor of varicose veins in both genders. The strong effect of family history on the risk of varicose veins in the literature is affected by differential misclassification bias.

TIIVISTELMÄ

Tutkimuksen tavoitteena oli arvioida seurantatutkimuksella joukkoa suonikohjujen mahdollisia riskitekijöitä yleisessä keski-ikäisessä väestössä. Tutkittuja tekijöitä olivat synnyttäneisyys, ehkäisypillereiden käyttö, hormonikorvaushoito, elämäntapatekijät ja itse raportoitu suonikohjujen sukuhistoria. Tarkoituksena oli arvioida myös eriävästä virheluokittelusta johtuvaa harhaa sukulaisten suonikohjujen itseraportoinnissa.

Viisivuotinen seuranta-aineisto kerättiin postitetuilla kyselylomakkeilla kolmelta tamperelaiselta ikäkohortilta. Kohdeväestönä olivat 40-, 50- ja 60-vuotiaat, yhteensä 6874 henkilöä. Tutkimuksen alussa vastausprosentti oli 81 % (5568 henkilöä). Vastanneille lähetettiin lähes samanlainen kyselylomake viisi vuotta myöhemmin. Vastausprosentti oli toisessa kyselyssä 88 % (4903 henkilöä). Kyselylomake sisälsi kysymyksiä terveydentilasta, elämäntavoista sekä omista ja lähisuvun suonikohjuista. Osa tutkimukseen vastanneista henkilöistä tutkittiin kliinisesti, mutta heidän lähisukulaisiaan ei. Riskin osoittamiseen käytettiin uusien suonikohjujen ilmaantuvuutta henkilöillä, joilla ei ollut suonikohjuja tutkimuksen alussa.

Uusia suonikohjuja ilmaantui enemmän ainakin kolme lasta synnyttäneille naisille kuin synnyttämättömille, ilmaantuvuuden vetosuhde, IOR 2,0 (95 %:n luottamusväli 1,0–3,9). Alkoholia viikoittain käyttävillä suonikohjujen ilmaantuvuus oli suurentunut verrattuna henkilöihin, jotka eivät käyttäneet alkoholia viikoittain, IOR 1,5 (1,05–2,3). Tulos oli tilastollisesti merkitsevä vain naisilla. Tupakoimattomiin henkilöihin verrattuna henkilöillä, jotka olivat tupakoineet yli vuoden ajan, sekä heistä niillä, jotka olivat tupakoineet runsaasti (≥15 savuketta päivässä), oli suurentunut riski saada suonikohjut, ensiksi mainituilla IOR 1,3 (0,9–1,8) ja jälkimmäisillä 1,8 (1,1–2,8). Päivittäinen lihan syöminen näytti vähentävän suonikohjuriskiä varsinkin naisilla, kun sitä verrattiin vähäiseen (0–2 annosta viikossa) lihan syömiseen. Päivittäisellä kuidun saannilla, ehkäisypillereiden käytöllä tai hormonikorvaushoidolla ei todettu vaikutusta suonikohjujen ilmaantuvuuteen.

Henkilöillä, joilla suonikohjujen sukuhistoria oli positiivinen, suonikohjuriski oli lisääntynyt verrattuna henkilöihin, joilla suonikohjujen sukuhistoria oli negatiivinen, IOR 1,6 (1,1–2,3). Kun miehet ja naiset analysoitiin erikseen, riski oli merkitsevästi lisääntynyt naisilla, IOR 1,8 (1,1–2,8), mutta ei miehillä, IOR 1,4 (0,7–2,6). Ilmaantuvuuden riskiarviot olivat selvästi matalampia kuin tutkimuksemme vastaavat vallitsevuustulokset (OR 6,6 miehillä ja OR 4,9 naisilla) sekä kirjallisuudessa yleensäkin esitetyt arviot poikkileikkaustutkimusten perusteella.

Henkilön oma suonikohjustatus tai muutos statuksessa oli yhteydessä siihen, miten henkilö raportoi lähisukulaistensa suonikohjuista. Esimerkiksi, jos henkilö

ilmoitti tutkimuksen alussa ettei hänen suvussaan ole suonikohjuja, mutta hänelle itselleen kuitenkin ilmaantui suonikohjut seurannan aikana, riski suonikohjuisen sukulaisen raportointiin seurannan lopussa kasvoi kuusinkertaiseksi (OR 6,0 (2,0–47,8)). Jos taas henkilö ilmoitti omaavansa suonikohjut sekä seurannan alussa että lopussa, riski suonikohjuisen sukulaisen raportointiin seurannan lopussa oli alle yksi (OR 0,8 (0,6–0,9)).

Johtopäätöksenä voidaan todeta, että naisilla monisynnyttäneisyys, alkoholin käyttö ja positiivinen sukuhistoria lisäävät suonikohjuriskiä, kun taas liharuoan käyttö saattaa vähentää sitä. Tupakointi on suonikohjujen todennäköinen riskitekijä molemmilla sukupuolilla. Kirjallisuudessa esitettyyn voimakkaaseen suonikohjujen sukuriskiin liittyy eriävä virheluokitteluharha.

1. INTRODUCTION

Primary varicose veins are a typical manifestation of chronic venous insufficiency. The etiology of varicose veins is still incompletely understood despite the fact that it is a very common disease affecting all ages from teenagers to elderly people. The prevalence of varicose veins varies substantially in different parts of the world, being highest in the western world; mostly from 10% to 30% in men and from 25% to 55% in women in population-based studies (Callam 1994, Beebe-Dimmer et al. 2005, Robertson et al. 2008). In population in middle to late adulthood (40–69 years) the incidence of varicose veins ranged from 9 to 19 per 1,000 person-years in men and from 19 to 26 per 1,000 person-years in women in follow-up studies from Finland and the USA (Brand et al. 1988, Mäkivaara et al. 2004).

The prevalence of varicose veins increases with age (Cesarone et al. 2002, Crique et al. 2003, Kroeger et al. 2004). Hence every way to prevent the disease in this aging world population is worthwhile. Other reported risk factors are female gender (Brand et al. 1988, Sisto et al. 1995, Crique et al. 2003, Carpentier et al. 2004), parity (Sisto et al. 1995, Criqui et al. 2007), positive family history of varicose veins (Cornu-Thenard et al. 1994, Scott et al. 1995, Lee et al. 2003) and obesity in women (Brand et al. 1988, Lee et al. 2003). There are also many hypothetical postulated risk factors such as diet and other lifestyle factors, occupation involving prolonged sitting or standing, and hormone medications, but the existing data is inconsistent for further conclusions. At the moment, it is assumed that the etiology of varicose veins is multifactorial, but the more specific role of both environmental and genetic factors in the development of varicose veins is not known (Ng et al. 2005, White and Ryjewski 2005, Raffetto and Khalil 2008). An understanding of the basis of varicose veins formation will provide possible tools for prevention or highlight new tools for treatment.

The knowledge of the risk indicators of varicose veins is mainly based on cross-sectional surveys conducted in a selected population (e.g. hospital or clinic patients or occupational groups of only one sex). The temporal relationship between the potential risk factor (cause) and the outcome (effect) is very important in estimating causality. In cross-sectional studies, the estimation of cause and effect is simultaneous and it is often unclear whether the hypothetical cause preceded the effect in time or the opposite. Follow-up studies do not have these problems because the incident cases of the disease are detected in subjects originally free of it and the data on the risk factors is collected at entry of the follow-up.

There are only a few follow-up studies on the causes of varicose veins. The Tampere Varicose Vein Study is one of the first population-based follow-up studies to examine varicose veins and their occurrence, risk factors and associations with other diseases. As a part of the study, the purpose of this thesis was to evaluate if female hormones, specific lifestyle factors and a positive family history of varicose veins are risk factors for varicose veins in a middle-aged population.

2. REVIEW OF THE LITERATURE

2.1 Definition and classification of varicose veins

Varicose veins are dilated subcutaneous veins three millimeters in diameter or larger, measured in an upright position (Eklöf et al. 2004). They are usually bilateral affecting both legs (75-76%) (Abramson et al. 1981, Maffei et al. 1986, Hirai et al. 1990, Komsuoglu et al. 1994) and when unilateral they are detected with the same frequency on each leg (Maffei et al. 1986, Hirai et al. 1990, Komsuoglu et al. 1994).

There was lack of a uniform classification system for chronic venous disorders until the 1980s when the first proposed reporting standards for publications dealing with venous disease were published (Anonymous 1988). Based on that report, the American Venous Forum developed a more detailed descriptive classification system, CEAP, for chronic venous disorders in 1994 and this was published in 25 journals and books (Eklöf et al. 2004). It was based on clinical manifestations (C), etiological factors (E), anatomic distribution of disease (A), and underlying pathophysiological findings (P) (Table 1) (Porter and Moneta 1995). In 2004 a revised version of the basic CEAP classification (Table1) and advanced CEAP classification was published (Eklöf et al. 2004).

Table 1. The basic CEAP classification system.

Clinical signs*	Class 0	No visible or palpable signs of venous disease
	Class 1	Teleangiectasies or reticular veins
	Class 2	Varicose veins (≥ 3mm in diameter)
	Class 3	Edema
	Class 4a	Pigmentation or eczema
	Class 4b	Lipodermatosclerosis or atrophien blanche
	Class 5	Healed venous ulcer
	Class 6	Active venous ulcer
Etiologic factors	Congenital, primary, secondary or no venous cause identified	
Anatomic distribution	Superficial, perforator, deep veins or no venous location identified	
Pathophysiologic findings	Reflux or obstruction, alone or in combination or no venous pathophysiology identifiable	

*Class supplemented by (S) for symptomatic or (A) for asymptomatic presentation

Before the CEAP consensus statement, the definition of varicose veins in different studies was diverse, making it difficult to compare the results of epidemiologic studies. One of the most used definitions has been according to Arnoldi (1957) “any dilated, elongated, or tortuous veins, irrespective of size” and the other from the Basle study, where varicosities were classified into three types (spiderwebs, reticular varices or trunk varices) and each of these into three grades of severity (da Silva et al. 1974).

2.2 Occurrence of varicose veins

2.2.1 Geographical distribution

The occurrence of varicose veins has been studied in general populations in Europe and the USA, but many prevalence studies are from other defined populations. There are only two other longitudinal follow-up studies on the incidence of varicose veins in adult population: the Framingham Study from the USA and the San Valentino Screening Project from Italy (Brand et al. 1988, Cesarone et al. 2002). (Table 2)

According to review articles, the prevalence of varicose veins ranges from 2% to 57% in men and from <1% to 73% in women (Beaglehole 1986, Callam 1994, Evans et al. 1994, Beebe-Dimmer et al. 2005, Robertson et al. 2008) and the incidence estimate is based on the Framingham Study with a two-year incidence rate of 39.4/1,000 person-years for men and 51.9/1,000 for women (Callam 1994, Robertson et al. 2008).

Europe and North America. In Finland, the prevalence of varicose veins reported earlier from the Tampere Varicose Vein Study population was 18% in men and 42% in women (Laurikka 1992, Laurikka et al. 1993). The incidence from the five-year follow-up of the same study was 8.5/1,000 person-years in men and 19.2/1,000 person-years in women (Mäkivaara et al. 2004, Mäkivaara 2008). Another population study from Finland, the Mini-Finland Health Survey, reported the prevalence of varicose veins diagnosed by a physician to be 7% in men and 25% in women aged 30 years and over (Sisto et al. 1995).

A study of general population at four locations in France (n=8,000) found a prevalence of varicose veins 30% in men and 51% in women (Carpentier et al. 2004). In Italy, in a follow-up study of a total population with 30,000 subjects the total prevalence of varicose veins was 7% (Cesarone et al. 2002). In the same study the incidence (new cases per year) of varicose veins was 0.22%. In Poland, 28% of the men and 35% of the women had varicose veins in a study on 40,095 participants aged 16–97 (Jawien et al. 2003).

In Switzerland, two studies were reported among employees (Guberan et al. 1973, da Silva et al. 1974). In the Basle Study of 4,422 chemical industry employees varicose veins of all types and grades were observed in 57% of the men and 68% of the women and severe forms of varicose veins in 4% of the study subjects (da Silva et al. 1974). Of 610 women working in department stores 29% suffered from varicose veins or reticular veins, but the prevalence varied significantly depending on the country of origin: After standardizing for age, the prevalence of varicose veins was significantly lower (20%) among the 154 women from Italy and Spain than among others (from Switzerland, France and other Central Europe) (Guberan et al. 1973).

The prevalence of varicose veins was studied in elderly persons over 60 years of age in Turkey, where the prevalence was 35% in men and 38% in women (Komsuoglu et al. 1994). In the Edinburgh Vein Study (n=1,566), the age-adjusted prevalence of trunk varices was 40% in men and 32% in women aged 18–64 years (Evans et al. 1999). In another study in the United Kingdom the prevalence of varicose veins was lower for men (17%), but the rate for women (32%) was the same as in the Edinburgh Vein Study (Franks et al. 1992).

In the Framingham Study, during 16 years of follow-up the incidence rate per 1,000 person-years was 19.7 in men and 25.9 in women aged 40–89 years in a general population of 3,822 subjects (Brand et al. 1988). In San Diego, California a cross-sectional study of a multiethnic sample of 2,211 people aged 40–79 years, current and retired employees of the University of California and the spouse of a randomly selected participant, reported 15% of the men and 28% of the women to have varicose veins (Criqui et al. 2003). In the Tecumseh Community Health Study, Michigan, the prevalence of any varicose veins in subjects aged 10–70+ (n=6,389) was 13% in males and 26% in females. In the same study the respective prevalence of varicose veins 2+ or greater i.e. “significant” varices was 7% and 17% (Coon et al. 1973).

Asia. In general population of Israel, the prevalence of varicose veins was 10% among men and 29% among women aged 15 and over (Abramson et al. 1981). The other studies from Asia are on populations subject to different selections. The highest prevalence of all kinds of varicosities (45%) was reported in females in a Japanese study (Hirai et al. 1990) and the lowest prevalence of varicose veins (1%) was reported in female government employees with a mean age of 27 years (Colin 1972). There are also data from five investigators who examined adult hospital patients in India and anecdotally reported prevalence of varicose veins ranging between <1 and 2% in men and between 0 and 1 percent in women (Burkitt et al. 1975).

Table 2. Studies (N>200) on the occurrence of varicose veins by geographical distribution.

Region	Country	N	Age at entry (years)	Population	Design	Result	Reference
Europe and North America	Finland	6874	40–60	General population	Cross-sectional	P=18% in men and 42% in women	Laurikka et al. 1993
		8000	≥30	General population	Cross-sectional	P=7% in men and 25% in women	Sisto et al. 1995
		4903	40–60	General population	Follow-up, 5 years	I=8.5/1000 in men and 19.2/1000 in women	Mäkivaara et al. 2004
	France	7432	42–53	Male employees	Cross-sectional	P=10% in men	Ducimetiere et al.1981
		8000	≥18	General population	Cross-sectional	P=30% in men and 51% in women	Carpentier et al. 2004
	Italy	1319	>65	General population	Cross-sectional	P=17% in men and 35% in women	Canonico et al. 1998
		30000	Any	General population	Follow-up, 6 years	I=2.2/1000	Cesarone et al. 2002
	Poland	40095	16–97	Outpatient clinic patients	Cross-sectional	P=28% in men and 35% in women	Jawien et al. 2003
	Switzerland	4422	20–70	Industrial employees	Cross-sectional	P=57% in men and 68% in women	da Silva et al. 1974
		610	≥15	Female store employees	Cross-sectional	P=29% in women	Guberan et al. 1973
	Turkey	856	≥60	General population	Cross-sectional	P=35% in men and 38% in women	Komsuoglu et al. 1994
	The UK	504	15–74	Female cotton workers	Cross-sectional	P=32% in women	Mekky et al. 1969
		2103	35–70	GP-patients	Cross-sectional	P=17% in men and 32% in women	Franks et al. 1992
		1566	18–64	General population	Cross-sectional	P=40% in men and 32% in women	Evans et al. 1999
	USA	6389	≥10	General population	Cross-sectional	P=13% in men and 26% in women	Coon et al. 1973
		3822	40–89	General population	Follow-up, 16 years	I=19.7/1000 in men and 25.9/1000 in women	Brand et al. 1988
		2211	40–79	University employees	Cross-sectional	P=15% in men and 28% in women	Criqui et al. 2003
Asia	Hong Kong	6250	NA	Government employment applicants	Cross-sectional	P=5% in men and 1% in women	Colin 1972
	India	677	18–65	Male railroad workers	Cross-sectional	P=25% in South and 7% in North India	Malhotra 1972
	Israel	4802	≥15	General population	Cross-sectional	P=10% in men and 29% in women	Abramson et al. 1981
	Japan	646	≥15	Patients, hospital staff and residents in elderly homes	Cross-sectional	P=34% in men and 45% in women	Hirai et al. 1990
	KSA	2350	≥18	Patients	Cross-sectional	P=14%	Bawakid et al. 2005
	Thailand	1000	Adults	NA	Cross-sectional	P=6%	Burkitt et al. 1976
South America	Brazil	1755	>15	Patients	Cross-sectional	P=38% in men and 51% in women	Maffei et al. 1986
	Peru	2084	>16	Patients	Cross-sectional	P<1%	Dalrymple and Crofts 1975

Africa	Egypt	467	15–74	Female cotton workers	Cross-sectional	P=6%	Mekky et al. 1969
	Mali	469	NA	Female population	Cross-sectional	P=3%	Rougemont 1973
	South-Africa	297	≥18	Female population	Cross-sectional	P=8%	Daynes and Beighton 1973
	Tanzania	342	NA	Rural villagers	Cross-sectional	P=1% in men and 2% in women	Burkitt et al. 1976
		1000	≥18	Outpatient clinic patients	Cross-sectional	P=6% in men and 5% in women	Richardson and Dixon 1977
Oceania	Cook Island	377	15–64	Pukapukas	Cross-sectional	P=2% in men and 4% in women	Beaglehole et al. 1975
		417		Rarotongas		P=16% in men and 15% in women	
	New Guinea	1457	≥20	Rural villagers	Cross-sectional	P=5% in men and <1% in women	Stanhope 1975
	New Zealand	721	15–64	Maoris	Cross-sectional	P=33% in men and 44% in women	Beaglehole et al. 1975
		356		Pakehas		P=20% in men and 38% in women	
	Tokelau Island	786	15–64	Population sample	Cross-sectional	P=3% in men and 1% in women	Beaglehole et al. 1975

P, prevalence; I, incidence; GP, General Practitioner; NA, not available; KSA, Kingdom of Saudi Arabia

South America. In Brazil, the prevalence of varicose veins was investigated in a population attending the University Health Center in Botucatu for routine examination or for any complaint; 38% of the men and 51% of the women had varicose veins (Maffei et al. 1986). In Peru, 2,084 patients aged over 16 were studied and three cases of varicose veins were found in the group of mestizo, none of Indian origin (Dalrymple and Crofts 1975).

Africa. In Egypt, the prevalence of varicose veins was 6% among women cotton workers (Mekky et al. 1969). It was 3% (11% when reticular veins were also included) in Mali among the female population (n=469) of ten villages studied (Rougemont 1973) and 8% in South Africa in the Transkei (n=297) in women aged 18 and over (Daynes and Beighton 1973). Both genders were studied in Tanzania, where 6% of African men and 5% of African women aged 18 and over (n=1,000) had varicose veins, the slight male predominance was due to the older ages of men in the study population (Richardson and Dixon 1977). In a rural area in Tanzania varicose veins were observed in 1% men and 2% women (Burkitt et al. 1976).

In addition, several authors have reported anecdotal evidence derived from their clinical observations, suggesting that varicose veins are uncommon in Africa: Williams (1974) worked in Uganda for 33 years and among the 100,000 patients he saw, not more than 50 had varicose veins. Coles (1974) stated that among 25,300 operations performed in 19 years in a rural hospital in Sierra Leone only 11 were because of varicose veins. Worsfold (1974) worked in Zambian hospital for 27 years and he thought he “could almost count on two hands the number of patients with varicose veins”. Milton-Thompson (1974), after 22 years experience in a hospital and among outpatients in Kenya, could recall three women with varicose veins and no men.

Oceania. In studies from the 1970s the prevalence of varicose veins was 33% (in men) and 44% (in women) in New Zealand Maoris, 20% and 38% in New Zealand Pakehas (people of European descent), 16% and 15% in people living in Rarotonga, 2% and 4% in Pukapuka and 3% and 1% on Tokelau Island (Beaglehole et al. 1975) and 5%/<1% in a rural area of northern New Guinea (Stanhope 1975).

To summarize, there is a striking geographic variation in the occurrence of varicose veins. Broadly, the prevalence of varicose veins in Europe and North America is around 10–30% in men and 25–50% in women, in Asia (excluding Japan) 1–25%, in Africa <1–6% and <1–15% in Polynesians (20–40% in people living in New Zealand). The studies from South America are too few to summarize. Moreover, the few studies on incidence show a wide variation from 0.2 to 2 per 100 person-years.

Geographic variation in the occurrence of varicose veins may be due to differences in population sampling (especially age, gender and racial mix), in varicose vein definition and diagnosis, and access to medical care. It can also be explained by a real effect of differences in lifestyle and genetic factors. Geographic variation is

usually construed as a strong indicator for the presence of environmentally induced variation (Khoury et al. 1993). However, geographic variation is consistent with genetic contribution as well (Khoury et al. 1993), and such does not elucidate the etiology of varicose veins.

2.2.2 Age differences

In the Framingham Study age had no obvious effect on the incidence of varicose veins (Brand et al. 1988). In the Tampere Varicose Vein Study the highest incidence was in the cohort of 50-year-olds compared to the cohorts of 40 and 60-year-olds, but the difference was statistically significant only in women (Mäkivaara et al. 2004).

In most studies the prevalence of varicose veins increased with age in both genders (Weddell 1969, Coon et al. 1973, da Silva et al. 1974, Abramson et al. 1981, Maffei et al. 1986, Laurikka et al. 1993, Evans et al. 1999, Cesarone et al. 2002, Criqui et al. 2003, Kroeger et al. 2004). The same was observed in the studies of male Indian railroad workers (Malhotra 1972) and Japanese women (Hirai et al. 1990). An Italian study among elderly people (their age ranging from 66 to 96 years) reported a similar prevalence throughout age classes (Canonico et al. 1998). However, a Turkish study on persons aged 60 or over found the prevalence of varicose veins to increase with age in men, but not in women; the prevalence was higher in the group of 70 to 79-year-olds compared to the group of 80+ year-old women (Komsuoglu et al. 1994).

To conclude, the incidence of varicose veins is quite stable throughout adulthood. The prevalence of varicose veins increases with age, because only a few are treated and because they are not lethal. However, it is somewhat contradictory that the highest incidence of varicose veins is around 2 per 100 person-years (as mentioned in Chapter 2.2.1.) and the prevalence of varicose veins is not higher than 17–38% in studies of elderly people (Komsuoglu et al. 1994, Canonico et al. 1998).

2.3 Risk factors of varicose veins

2.3.1 Gender

The incidence of varicose veins was higher in women than in men aged 40–79 years, but no longer in the group aged 80–89 years in the Framingham Study (Brand et al. 1988). In Finland the incidence rate was significantly higher in women in all cohorts studied (from 40 to 60-year-olds) (Mäkivaara et al. 2004).

Earlier studies also showed a higher prevalence of varicose veins in women than men (Weddell 1969, Coon et al. 1973, Abramson et al. 1981, Maffei et al. 1986, Franks et al. 1992, Laurikka et al. 1993, Sisto et al. 1995, Canonico et al. 1998, Criqui et al. 2003, Carpentier et al. 2004, Kroeger et al. 2004, Bawakid et al. 2005), but in some of them the difference between genders was not statistically significant (Beaglehole et al. 1975, Komsuoglu et al. 1994, Cesarone et al. 2002). There are also some studies which suggest that the prevalence of varicose veins is higher in men (Colin 1972, Stanhope 1975, Evans et al. 1999, Chiesa et al. 2005a, Chiesa et al. 2007).

2.3.2 Weight and height

In the Framingham Study the incidence of varicose veins was higher among women who were obese than those who were of normal weight (Brand et al. 1988). In the same study the incidence was also higher for obese men, but the difference was not statistically significant. A follow-up study in the Netherlands also found a higher risk of varicose veins in the overweight group compared to the control group in women but not in men (Seidell et al. 1986). Only men were studied in a follow-up study in the USA, which did not find obesity to increase the risk for varicose veins (Scott et al. 2004).

Many cross-sectional studies have shown an association between obesity and varicose veins for both sexes (Laurikka et al. 2002) or at least for women (Abramson et al. 1981, Sisto et al. 1995, Canonico et al. 1998, Lee et al. 2003). However, the studies in Switzerland (da Silva et al. 1974), Turkey (Komsuoglu et al. 1994), France (Carpentier et al. 2004) and Germany (Kroeger et al. 2004) did not find an obvious association between obesity and the prevalence of varicose veins in either sex, neither did the two studies in Switzerland and Japan including only female subjects (Guberan et al. 1973, Hirai et al. 1990).

Increasing height showed a significant relationship with trunk varices in the Edinburgh Vein Study both in males and females (Lee et al. 2003). In the Tampere Varicose Vein Study it was also an independent determinant for varicose veins in both sexes (Laurikka et al. 2002). Another Finnish study (Sisto et al. 1995) and a French study (Carpentier et al. 2004) found height significant only in women. No association was reported in the studies from Turkey (Komsuoglu et al. 1994), Switzerland (Guberan et al. 1973) and Japan (Hirai et al. 1990).

2.3.3 Female hormones

There are physiologic states, such as pregnancy and menopause and iatrogenic states because of hormone medications, in which the level of female hormones in the circulation is far from normal and those states have been associated with varicose veins.

Parity. In the Framingham Study women who had had two or more pregnancies had a higher age-adjusted incidence of varicose veins than those who had had one or no pregnancies, but without statistical significance (Brand et al. 1988). Also, the majority of earlier prevalence studies have found a risk between varicose veins and parity (Arnoldi 1957, Mekky et al. 1969, Weddell 1969, Maffei et al. 1986, Sadick 1992, Komsuoglu et al. 1994, Jawien et al. 2003, Criqui et al. 2007). Some of the studies reported already one pregnancy to increase the risk for developing varicose veins (Abramson et al. 1981, Stvrtinova et al. 1991, Canonico et al. 1998, Carpentier et al. 2004), whereas in the other studies more than one delivery had a significant influence (Hirai et al. 1990, Kroeger et al. 2004). In an Italian study the odds ratio was twofold in women with at least one pregnancy compared to nulliparous women (Carpentier et al. 2004). In Finland the multi-adjusted odds ratio for varicose veins increased from 1.4 (95% CI: 1.0–1.9) to 3.0 (95% CI: 2.3–4.1) in women with one child to women with up to five children when compared to nulliparous women (Sisto et al. 1995).

A minority of the prevalence studies did not find a significant association between the prevalence of varicose veins and childbirth (Weddell 1969, Coon et al. 1973, Guberan et al. 1973). Neither did the Edinburgh Vein Study find a risk between pregnancy and trunk varicosities, but less severe changes in veins were more common in women with a history of pregnancy (Lee et al. 1999).

Oral contraceptives. In the USA Sadick (1992) reported that patients with telangiectatic or varicose veins used contraceptive pills more often than those in the control group. The others found no association (Scott et al. 1995, Sisto et al. 1995, Lee et al. 2003, Kroeger et al. 2004).

Hormone replacement therapy. The results of studies on the association between menopausal hormone replacement therapy and varicose veins are inconsistent. The use of hormonal therapy increased the risk of chronic venous insufficiency (class 1 to 4 of CEAP) in a study on the Saudi adult population (Bawakid et al. 2005). Sisto and associates (1995) observed a statistically significant difference in the age-adjusted prevalence of varicose veins in women taking hormone replacement (aged 50 years and over) compared to women not exposed (35% vs. 27%). In the Edinburgh Vein Study the use of hormone replacement therapy showed a significant decreased risk of trunk varices (Lee et al. 2003). In a French study of risk

factors of varicose veins estrogen therapy was only mentioned not to be significant (Carpentier et al. 2004).

Others. A higher risk for varicose veins was related to later age at menarche in an old Danish study (Arnoldi 1957), whereas a Swiss study could not find any association between the prevalence of varicose veins and the age at menarche (Guberan et al. 1973). According to Brand et al. (1988) women with varicose veins were significantly older at menopause. Two other studies could not confirm the relationship (Abramson et al. 1981, Lee et al. 1999).

In an Italian study of menopausal women (n=104) the women with serum levels of estradiol in the upper tertile of the frequency distribution had a significantly higher prevalence of varicose veins than the women in the two lowest tertiles (Ciardullo et al. 2000). A recent study on 21 varicose (CEAP≥2) and 13 healthy men demonstrated a changed serum estradiol/testosterone ratio among men with varicose veins compared to healthy men (Kendler et al. 2009).

2.3.4 Occupation and physical activity

Significant associations were found with a standing posture at work and varicose veins in both sexes (Abramson et al. 1981, Tuchsen et al. 2000, Kroeger et al. 2004) or in women (Mekky et al. 1969, Sisto et al. 1995, Jawien et al. 2003, Lee et al. 2003), but not by all authors (Weddell 1969, Maffei et al. 1986). Working in a standing position was even associated with subsequent hospitalization due to varicose veins for both men and women in the Danish study (Tuchsen et al. 2000). Work involving heavy lifting was also related to the higher prevalence of varicose veins in one study (Weddell 1969), but not in another (Lee et al. 2003).

A study from Scotland found mainly the seated position at work to decrease the risk for trunk varices in women (Lee et al. 2003), whereas a study from Finland did not report any association between a sitting posture at work and varicose veins in either gender (Sisto et al. 1995).

In the Framingham Study physical activity was assessed by the hours spent daily resting and doing sedentary, light, moderate, and heavy activities (Brand et al. 1988). Compared to subjects without varicose veins, subjects with varicose veins had lower levels of physical activity. In a French study subjects were classified into two groups according to their regular exercise activity: those having less than one session and those with at least one session of exercise per week (Carpentier et al. 2004). Lack of exercise was a risk factor of varicose veins in men but not in women. A study in the former Czechoslovakia reported prevalence of varicose veins of all types in women (Stvrtinova et al. 1991). The prevalence was lower in those who were physically active at least once a week compared to those with no physical activity, but the

difference was not statistically significant. “Physical activity” was not specified in that study.

2.3.5 Dietary factors, alcohol consumption and smoking

Diet. Some studies reported diets deficient in fiber-rich plant foods and consequent constipation as risk factors for varicose veins (Cleave 1959, Dodd 1964, Burkitt 1976) whereas others did not find constipation to be a risk factor for varicose veins (Mekky et al. 1969, Abramson et al.1981, Canonico et al.1998, Criqui et al. 2007). In the Edinburgh Vein Study there was no association between the prevalence of trunk varices and dietary fiber intake in either sex (Lee et al. 2001, Lee et al. 2003). One study reported a significantly higher average calory intake in men with varicose veins, but did not find a significant difference in the distribution of various nutrients used (Ducimetiere et al. 1981).

Alcohol consumption. In a case-control study conducted in France alcohol abuse indicated a higher risk of lower limb venous insufficiency, but when adjusted for other potential risk factors, the result was no longer statistically significant (Gourgou et al. 2002). The two studies on varicose veins did not suggest alcohol consumption to be a significant risk factor for varicose veins (Carpentier et al. 2004, Scott et al. 2004).

Smoking. A longitudinal follow-up survey on men in Boston reported current smokers to be more likely to develop varicose veins than non-smokers, RR 1.3 (95% CI: 1.01–1.6) (Scott et al. 2004). In the Framingham Study men with varicose veins had higher smoking rates than those without varicose veins, but the difference was not observed in women (Brand et al. 1988). In a cross-sectional study from France smoking men had more varicose veins than men who did not smoke (Ducimetiere et al. 1981). A case-control study (n=3,612) carried out in France reported lower limb venous insufficiency to be significantly associated with tobacco smoking with dose-effect relation in both genders. Most of the other studies observed no association between varicose veins and smoking (Malhotra 1972, Abramson et al. 1981, Hirai et al. 1990, Franks et al. 1992, Lee et al. 2003, Carpentier et al. 2004, Komsuoglu et al. 2004).

There are also two studies with unexpected results. In a German study of risk factors of varicose veins smoking indicated a protective effect on varicose veins in both genders (Kroeger et al. 2004), whereas in a Finnish study odds ratio <1 was observed only in women (Sisto et al. 1995). One possible explanation for the result of the German study is the design; subjects who had had treatment for varicose veins were left out of the risk factor analysis comparing subjects with and without varicose veins.

2.3.6 Heredity

A familial predisposition to varicose veins has been proposed for at least a century. Most of the information about the potential heredity of varicose veins has been obtained by taking a family history. However, responses to the questions about family history may be biased for many reasons. Family members were examined only in two studies on varicose veins (Weddell 1969, Cornu-Thenard et al. 1994) and one on sapheno-femoral incompetence (Belcaro 1985), the others relied on the responses of the study subjects.

Clinically diagnosed varicose veins in family members. In a French study 134 families were examined: 67 varicose veins patients and their parents and 67 controls and their parents. The prevalence of varicose veins for a person was 90% when both parents suffered form varicose veins, 25% in males and 62% in females when one parent was affected, and 20% when neither parent was affected. (Cornu-Thenard et al. 1994)

In a Welsh study subjects and their over fifteen-year-old first-degree relatives, in total 76 families, were examined. 23% of the relatives of subjects with clinically varicose veins had varicose veins, while 14% of the relatives of subjects without varices had them. However, the author did not consider the result conclusive because of the small number of families studied. (Weddell 1969)

Belcaro (1986) assessed saphenofemoral incompetence in 47 young asymptomatic subjects with a positive family history of varicose veins (one or both parents had varicose veins in the examination) and in 32 controls with a negative family history. The prevalence of incompetence of the sapheno-femoral junction was higher in subjects with positive family history of varicose veins compared to those with negative one. Unfortunately the study lacks many essential details to merit serious attention.

Self-reported family history. The majority of earlier studies showed self-reported positive family history to be a risk factor for varicose veins (Mekky 1969, Hirai et al. 1990, Stvrtinova et al. 1991, Sadick 1992, Schultz-Ehrenburg et al. 1992, Komsuoglu et al. 1994, Scott et al. 1995, Jawien 2003, Lee et al. 2003, Carpentier et al. 2004, Kroeger et al. 2004, Criqui et al. 2007) and chronic venous insufficiency (Gourgou et al. 2002, Bawakid et al. 2005, Chiesa et al. 2005b). However, the risk estimates varied considerably.

In the Edinburgh Vein Study subjects with trunk varices reported a family history of varicose veins more often than those without varicose veins, multi-adjusted odds ratio 1.5 (95% CI: 1.03–2.3) in men and 2.2 (95% CI: 1.4–3.4) in women (Lee et al. 2003). Some higher ratios were found in the San Diego Population Study, where the multi-adjusted odds ratio in subjects with varicose veins (C2) was 2.9 (95% CI:

1.8–4.6) in men and 2.3 (95% CI: 1.8–3.1) in women (Criqui et al. 2007). In a French population-based study the corresponding ratios were 3.5 (95% CI: 1.9–6.5) and 3.5 (95% CI: 2.4–5.1), respectively (Carpentier et al. 2004). Still higher adjusted odds ratios for family history of venous insufficiency were observed in patients with venous insufficiency in a case-control study from France; OR 7.2 (95% CI: 4.6–11) in men and 7.7 (95% CI: 5.9–9.9) in women (Gourgou et al. 2002). In a German study the odds ratio decreased from 5.2 (95% CI: 2.3–7.3) in case of varicose veins in both parents, and 3.7 (95% CI: 3–4.6) in case of paternal varices to only 2.8 (95% CI: 2.4–3.3) in case of maternal varices only (Kroeger et al. 2004).

Family history and early and preclinical stages of varicose veins were studied in the longitudinal Bochum Study. Pupils aged 10 to 12 years old at entry were examined at the age of 14 to 16 years and again at the age of 18 to 20 years. Only a weak association was reported between varicose veins and family history. Isolated refluxes were found at the saphenofemoral junction before visible varicose veins. (Schultz-Ehrenburg et al. 1992)

In contrast to the above-mentioned risk trend an Israeli study did not find a significant association with parental consanguinity and varicose veins when age and sex were controlled for (Abramson et al. 1981). Neither did an Indian study establish a hereditary association, but there a large majority of the subjects were unable to answer to the question about the family history (Malhotra 1972).

Inheritance. Almost as long as the hypothesis of the genetic predisposition to varicose veins has existed, the question of the mode of inheritance has been discussed. Arnoldi (1958) proposed the assumption of dominant heritance, whereas Troisier and Bayon (1937) found their observations more in line with a recessive argument. Niermann (1964) reported a higher degree of concordance between monozygotic twins (75%) than between dizygotic twins of the same sex (52%), although the difference was not statistically significant as the numbers involved (12 monozygotic and 25 dizygotic pairs of the same sex) were too low. However, because no simple genetic mechanism was found to account for the findings Hauge and Gundersen (1969) proposed the hypothesis of polygenic inheritance. They assumed that the risk of varicose veins in a person is increased if a parent or sibling is affected, and especially if the affected relative is a male with early onset of varicose veins. Matousek and Prerovsky (1974) also studied the hypothesis of multifactorial inheritance and estimated the heritability of the condition to be about 50% and slightly higher for males than females.

The current consensus is that both environmental and genetic factors are associated with the development of varicose veins (Ng et al. 2005, White and Ryjewski 2005, Raffetto and Kahlil 2008). Recently a British genetic twin study suggested one candidate gene on chromosome 16 (FOXC2) to be implicated in the development of varicose veins (Ng et al. 2005). Another study reported FOXC2 to be important for the normal development and maintenance of venous and lymphatic

valves (Mellor et al. 2007). Moreover a German twin study determined the heritability of venous function and indicated a strong genetic influence of the venous function (Brinsuk et al. 2004).

2.3.7 Other potential risk factors of varicose veins

There are contradictory reports on the association between *education* and varicose veins. Lower level of education was not a risk factor for varicose veins in the follow-up design of the Tampere Varicose Vein Study (Mäkivaara et al. 2004). Parallel results were reported from cross-sectional studies on men in the USA (Scott et al. 2004) and on both genders in France (Carpentier et al. 2004). In the Edinburgh Vein Study lower level of education was significantly associated with an increased risk for trunk varices in men, but not in women (Lee et al. 2003). However, significant associations were reported with lower *social class* and varicose veins in French men (Ducimetiere et al. 1981), but not in the above-mentioned Scottish study (Lee et al. 2003).

An association between varicose veins and *arterial disease* and *congestive heart failure* was reported in the Tampere Varicose Vein Study (Mäkivaara 2008, Mäkivaara et al. 2008). Japanese investigators found *periodontitis* to be a risk factor for the development of varicose veins (Kurihara et al. 2007). They observed oral bacteria colonization in venous valves and assessed it by means of direct infection result to valvular incompetence. There is also an association between varicose veins and *deep venous thrombosis*, but the direction of the association is obscure. Deep venous thrombosis dilates the vein in response to proximal venous obstruction and causes valvular incompetence and reflux (Killewich et al. 1989), which could predispose to varicose veins. Saarinen et al. (1999) found a reverse association, where varicose veins were independent risk factors of deep vein thrombosis. However, the varicose veins appearing after deep venous thrombosis are classified as secondary and are not discussed further in the present study involving primary varicose veins.

2.4 Pathophysiology of varicose veins

Varicose veins are a common manifestation of chronic venous insufficiency. The four typical findings of varicose veins include venous hypertension, reflux, incompetent valves and vein wall dilation. Pathologic reflux may occur in the tributary veins, saphenofemoral and saphenopopliteal junctions, deep venous system or perforators, but the base mechanism explaining where and how this disease process begins and progresses remains undiscovered.

The primary structural changes in the valves may start the pathophysiolocial process of varicose veins through progressive reflux to the secondary changes in the vein wall (Raffetto and Khalil 2008) or alternatively, or in the same time, the valves may become incompetent secondary to vein wall abnormality near the valve junctions predisposing to venous dilation, and causing the reflux (Cooper et al. 2003, Elsharawy et al. 2007, Raffetto and Khalil 2008).

Recent studies support the latter theory and have evinced different reasons for the weakness of the vein wall. Explanations evinced include endothelial cell dysfunction (Somers and Knaapen 2006, Raffetto and Khalil 2008), changes of the smooth muscle cells and extracellular matrix (collagen, elastin, proteoglycans, and glycoproteins) (Travers et al. 1996, Wali et al. 2002, Elsharawy et al. 2007), chronic inflammation (Raffetto and Khalil 2008) and abnormalities in the content and activity of matrix metalloproteinases (MMPs) (Gillespie et al. 2002, Kowalewski et al. 2004, Hobeika et al. 2007) and their tissue inhibitors (TIMPs) (Raffetto and Khalil 2008).

2.4.1 Female hormones

The effects of estrogen are generally mediated by specific receptors, which act as transcription factors, regulating gene expression when they are activated by estrogen binding. By that mechanism estrogen affects the proliferation of vascular smooth muscle cells and the facilitation of angiogenesis (Gungor et al. 2009). Another rapid, “non-genomic” pathway of estrogens has been reported. One of its effects is endothelium-dependent vasodilatation in the arteries (Gilligan et al. 1994, Gungor et al. 2009). Two subtypes of the human estrogen receptor have been identified (ER-alpha and ER-beta) (Simoncini et al. 2004). Knaapen and associates (2005) reported that smooth muscle cell hypertrophy in varicose veins correlated with the expression of estrogen receptor-beta.

Progesterone and progestins (the synthetic forms of progesterone) act by binding to progesterone receptors (Wei and Horwitz 1985). Both genomic and non-genomic effects have been demonstrated, however, the effects on the cardiovascular system are unclear (Gungor et al. 2009). Either estrogen or progesterone receptors have been found in peripheral veins (Bergqvist et al. 1993). Mashiah et al. (1999) reported more estrogen and progesterone receptors in varicose segments of saphenous vein compared to adjacent non-varicose segments of the same vein.

2.4.2 Diet, alcohol and smoking

A low-fiber diet and concomitant constipation have been hypothesized to contribute to the development of varicose veins by two different mechanisms: Straining at stool could increase the intra-abdominal pressure and lead to valvular incompetence or overloaded colon could press the iliac veins and cause obstruction of venous return (Cleave 1959, Burkitt et al. 1976).

Alcohol has dose-dependent beneficial and harmful vascular effects, but the mechanisms that could explain the dual effects are not known. The ingestion of alcohol causes immediate vasodilation and decreasing of blood pressure, which is followed by a rebounding elevation of blood pressure, and alcohol drinking increases the risk of chronic hypertension (Bau et al. 2005). However, chronic hypertension has not been associated with an increased risk of varicose veins (Mäkivaara et al. 2008). Alcohol-induced endothelial damage or protection has been related to the synthesis or action of several markers, such as nitric oxide, cortisol, endothelin-1, adhesion molecules, tumor necrosis factor alpha, interleukin-6, C-reactive protein, and hemostatic factors (Bau et al. 2007).

Long-term smoking has harmful effects on the venous system, but conclusive evidence linking one chemical substance or a combination of these in smoke to vasculotoxity is not yet available. At least carbon monoxide, nicotine and oxidative damage are known to have harmful effects on endothelial structure and functions. (Jonas et al. 1992, de Sousa et al. 2005). Impaired endothelium-dependent vasodilatation responsiveness has been reported in the arteries (Neunteufl et al. 2002, de Sousa et al. 2005) and veins (Chalon et al. 2000, de Sousa et al. 2005).

3. AIMS OF THE STUDY

The main aim of the present study was to evaluate potential risk factors for varicose veins by a longitudinal follow-up study in a general middle-aged population.

The detailed objectives of the study were:

1. To establish the effect of female hormones on varicose veins by evaluating the role of parity, use of hormone replacement therapy and use of oral contraceptives on the incidence of varicose veins in women. (I)
2. To assess if there is an association between selected lifestyle factors (daily bread consumption, weekly meat consumption, weekly alcohol consumption and smoking) and the occurrence of varicose veins. (II)
3. To estimate if subjects with positive family history of varicose veins have a higher risk of developing varicose veins compared to subjects with negative family history, and to describe misclassification bias in self-reporting of family history in cross-sectional studies. (III, IV)

4. MATERIAL AND METHODS

4.1 Study population and data collection

The Tampere Varicose Vein Study comprised three complete age-cohorts of residents of the city of Tampere in Finland (population 171,307 in 1989) born respectively in 1929, 1939 and 1949, and identified from the National Population Registry. Thus the members of the three different cohorts were 40, 50 or 60 years old at the beginning of the study in 1989. The original target population consisted of 6,874 people, 3,284 men and 3,590 women (Figure 1). They were mailed a self-administered questionnaire in September, 1989. To those who did not respond to the first questionnaire, a new questionnaire was sent from one to two months later in order to get as a high a response rate as possible. The questionnaire was returned by 5,681 subjects, but 113 responses were excluded because of missing information on varicose veins. The rest, a total of 5,568 subjects were regarded as the target population of the five-year follow-up and they were mailed an almost identical questionnaire in 1994. Due to death during follow-up 139 subjects could not be contacted and 78 subjects could not be identified in the registry. Also, in 1994 a new questionnaire was sent to those who did not respond to the questionnaire in the desired time.

The questionnaires in both years were, for the most part, similar and included items on sociodemographic factors, varicose veins, dietary habits, smoking status, consumption of alcohol, parity, family history of varicose veins, physical activity, use of medications and selected diseases diagnosed by a doctor. The questionnaires are provided in the Appendices.

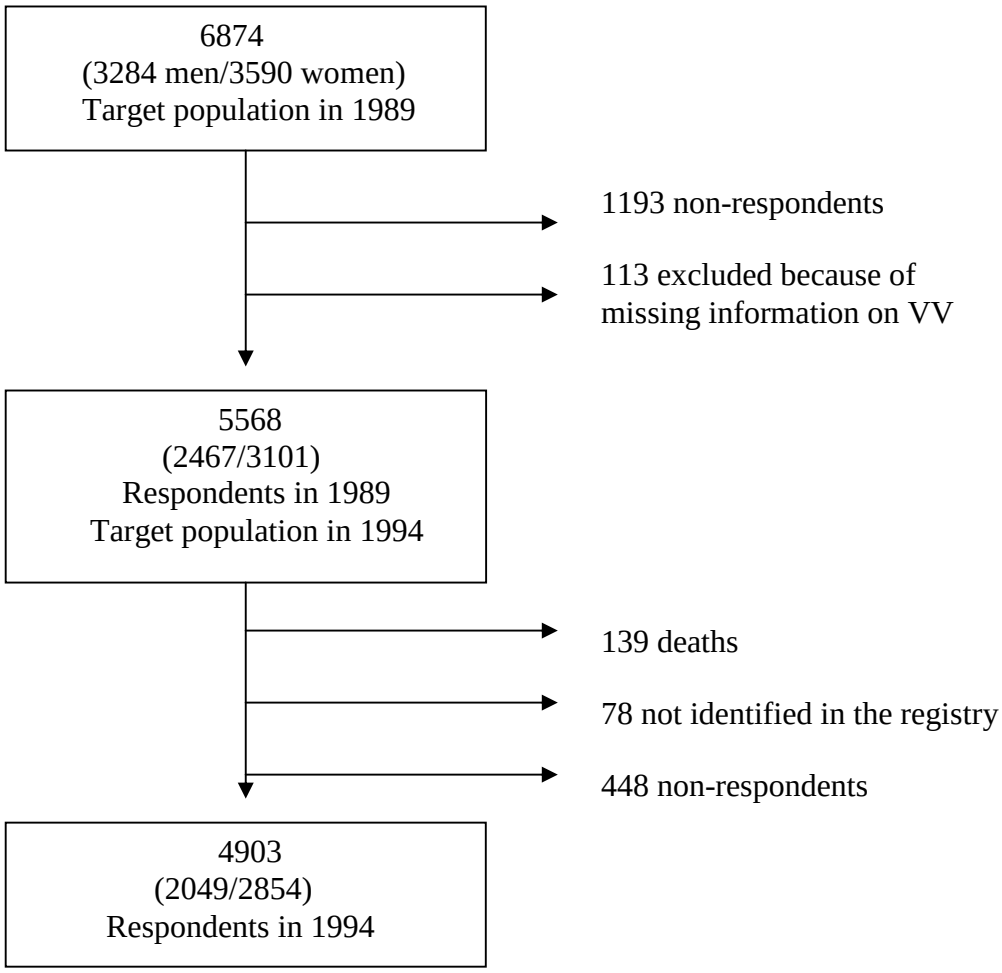

Figure 1. Participation in the Tampere Varicose Vein Study in 1989 and in 1994.

4.2 Survey methods

4.2.1 Definition of varicose veins

Varicose veins were defined as "clearly visible, dilated, tortuous, and possible prominent subcutaneous veins of the lower extremities". "Clearly visible" was added to Arnoldi's definition (Arnoldi 1957) to help the subjects rule out any invisible leg complaints. The definition corresponds to class 2 in the Clinical-Etiologic-Anatomic-Pathophysiologic (CEAP) classification system (Eklöf et al. 2004).

Clinical examination. The definition was tested in 1990 on a random sample of 166 subjects in the cohort born in 1939. They were invited for an examination to the outpatient clinic of the Department of Surgery, Tampere University Hospital. The

subjects were examined by a surgeon (J.L.) in a warm room by inspection of the lower extremities and Trendelenburg tests with continuous wave Doppler reflux verifications. The surgeon was blind to respondents' replies to the varicose vein question. All subjects with visible varicose veins were graded as varicose cases except those with telangiectasia as the only finding. In estimating validity, the surgeon's assessment was taken as the standard. Overall sensitivity and specificity were 0.93 and 0.93 in men and 0.92 and 0.91 in women. The estimates were poorer among subjects reporting positive family history of varicose veins (0.91 and 0.83) than among those with negative or uncertain family history (0.95 and 0.98) (Laurikka et al. 1995).

4.2.2 Assessment of risk factors

Parity, use of contraceptive pills, use of hormone replacement therapy, daily bread consumption, weekly consumption of meat products, alcohol consumption, smoking and positive family history of varicose veins were the variables studied as potential risk factors of varicose veins in this study and recorded at the beginning of follow-up (except regarding the use of contraceptive pills, which only elicited in 1994). Based on self-reported data from the questionnaires the risk factors were considered as follows.

Parity was defined as the number of births, also the year of the first birth was recorded. Women were classified into four groups according the number of births; 0, 1, 2 and 3 or more. Subjects using hormone replacement therapy were regarded as users of that medication, and others as non-users. In 1994 all respondents who reported ever having used contraceptive pills were classified as users. Duration of contraceptive pill use was also recorded. Bread consumption was elicited as slices of bread per day and classified into three categories: 0–2, 3–4 or >4 slices of bread per day. Consumption of meat products was elicited as a number of meals including meat or sausages per week and likewise classified into three categories: 0–2, 3–6 and >6 meals of meat or sausages per week. Subjects were defined as alcohol users if they reported weekly alcohol consumption. Those using alcohol "not at all or occasionally" were defined as non-users. Subjects were classified as smokers if they had ever smoked cigarettes, cigars or pipes for longer than one year, including also ex-smokers.

Family history of varicose veins was used as an indicator of heredity. This was elicited regarding close relatives including parents, grandparents and siblings. Family history was considered positive if at least one parent or sibling was affected. There was a response option "I do not know" and those subjects were regarded as uncertain.

4.2.3 Assessment of confounding factors

Age (I, II, III), sex (I, II, III), body mass index (BMI) (I, II, III), education (I, II) and parity (II) were treated as confounding factors. Body mass index was calculated by dividing the weight (kg) by the square of height (m^2) and respondents were classified as underweight or normal weight vs. overweight with 25kg/m^2 as the cut-off point. Level of education was elicited only in the questionnaire of 1994 and was used as a binary variable: comprehensive and vocational school were classified as lower education level, whereas university, college and high school were determined as higher education level. As a potential confounding factor parity was classified similar to that in the risk factor analysis (see 4.2.2.).

4.3 Statistical methods

In this study the incidence of varicose veins and more specifically the multivariate-adjusted incidence odds ratio (IOR) was used as an indicator of effect. Incidence observes the chronological order of cause and effect, which makes it primary indicator of effect in the observational studies of risk factors estimating causality. The prevalence odds ratio was calculated to enable comparison with earlier studies, which are mostly cross-sectional.

The length of follow-up was five years (an assumption based on questionnaire mailing times). The incidence of varicose veins was calculated in those initially free of varicose veins at entry, by dividing the number of new cases of varicose veins occurring during follow-up by the number of person-years of follow-up. The new varicose vein cases were assumed to appear at the midpoint of the five-year follow-up, i.e. their follow-up time was regarded as 2.5 person-years. The incidence rates were expressed as number of new cases per 1,000 person-years.

The prevalence of varicose veins was defined as the ratio of subjects ever having had varicose veins to all other subjects with the data on varicose veins and the variable in question at entry, i.e. in 1989, and it was shown in percentages (%). The prevalence of varicose veins by lifestyle factors and family history included only subjects who responded in both study-years, whereas those responding only in 1989 were also included in the prevalence of varicose veins by parity, OC and HRT use.

Multiple logistic regression analysis was performed to find the independent effects of risk factors of varicose veins. The adjusted odds ratios for incidence (IOR) and prevalence (OR) were presented with 95% confidence intervals (CI) and were calculated by software packages SPSS Version 10.1 (I, III) and Version 16.0 (II, IV).

Subjects with missing data on specific characteristics were excluded from the corresponding analyses. 95% conficence intervals not including 1.0 were regarded as statistically significant**.**

The effect of bias due to misclassification in the ascertainment of family history of varicose veins was assessed by consistency of the data on family history classified according to subject's self-reported varicose veins. The study population was stratified into four groups by own varicose veins (O(·,·) defined by – (without) or + (with) varicose veins at entry and at the end of follow-up; number of those reporting varicose veins neither at entry nor at the end of follow-up O(–,–), those reporting varicose veins both at entry and at the end O(+,+), those reporting no varicose veins at entry but varicose veins at the end O(–,+) and those vice versa O(+,–). Furthermore, in each group reported family history at entry and at the end of follow-up was expressed correspondingly as family frequencies; F(–,–), F(+,+), F(–,+) or F(+,–). E.g. F(–,–) is the number of subjects reporting no family members with varicose veins either at entry or at the end of the follow-up. Kappa coefficient was used to estimate the consistency of responses to the family history question between the two questionnaires in each of the O groups. Those uncertain about varicose veins or family history were left out. Kappa with 95% confidence intervals was calculated by StatXact version 4.0.1. The odds of having family members with varicose veins at entry was compared to the odds of having family members with varicose veins at the end and the association was estimated as the odds ratio from the discordant pairs, OR= F(+,–)/F(–,+) and tested by McNemar´s test in each of the four groups O(·,·). Exact Fisher's 95% confidence intervals for that ratio were calculated by WinEpi Describe version 1.55 Copyright J.H. Abramson 2004–2006.

4.4 Ethical aspects

The ethics committee of Tampere University Hospital approved the study, which also complies with the principles of the Declaration of Helsinki. The study protocol was also approved by the Ethics Committee of the City of Tampere.

5. RESULTS

5.1 Participation rates and data

At baseline, in 1989, three age-cohorts of residents of Tampere city were mailed the questionnaire. The response rate was 81.0%, 75.1% (n=2,467) among men and 86.4% (n=3,101) among women distributed by age-cohort as shown in Figure 2. To this follow-up target population an almost identical questionnaire was sent five years later. The response rate to the second questionnaire was 88.1%, 83.1% (n=2,049) among men and 92.0% (n=2,854) among women.

Follow-up respondents and those lost from follow-up were equal according to varicose vein status in men, but not in women. In the group of respondents a higher percentage of the women reported varicose veins (42.7% vs. 33.0%). Compared to follow-up participants, those lost from follow-up were more often smokers (75.1% vs. 66.6% in men and 40.7% vs. 34.1% in women), alcohol users (73.4% vs. 70.4% in men and 40.5% vs. 38.3% in women), and had lower bread consumption (≤4 slices) per day (48.7% vs. 44.4% in men and 61.9% vs. 58.4% in women). Those men who responded consumed more meat meals (>4) a week (50.5% vs. 46.6%), whereas women responders and non-responders were almost alike (34.2% vs. 34.8%).

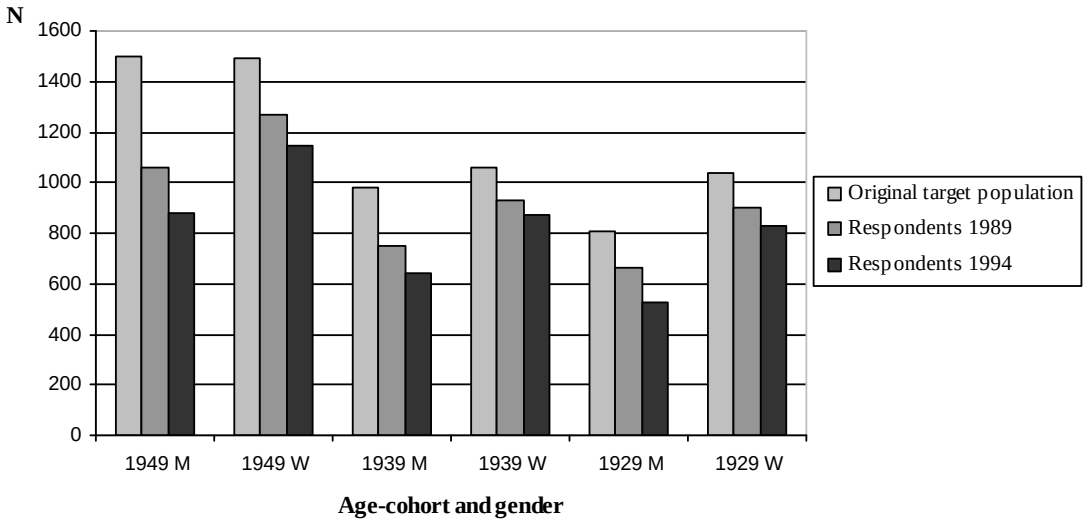

Figure 2. Number of men (M) and women (W) and their participation by age-cohort and gender in 1989 and 1994.

At the beginning of the study 18.1% of the men and 41.9 % of the women reported varicose veins, whereas 2.7% of the men and 4.5% of the women were uncertain. Incidence of varicose veins was studied in subjects responding in both evaluations and did not have varicose veins at entry (n=1,253 men and 1,147 women). 157 (52 men and 105 women) of them developed varicose veins during the five-year follow-up. The incidence of varicose veins in the population was 13.5 (per 1,000 person-years).

The majority of the population belonged to the youngest cohort (Table 3). The greatest difference between men and women in the various lifestyle factors was in weekly alcohol consumption and smoking. In the incidence study 70.2% of the men reported weekly alcohol consumption and 63.3% a positive smoking history, the corresponding percentages in women were 41.7% and 34.0%. The information on confounding factors and risk factors was missing for 0–2.6% of the subjects (Table 3).

5.2 Female hormones and the occurrence of varicose veins (I)

The prevalence and incidence of varicose veins in relation to parity, oral contraceptives and hormone replacement therapy use are summarized in Table 4. At entry 82.3% of the 2,948 women reported at least one and 22.8% three or more pregnancies, in the incidence study the rates were 80.2% and 18.7% (Table 3) respectively. The prevalence of varicose veins increased with the number of births; 33.5% in those with no births to 54.6% in those with three of more births (Table 4). The same was confirmed in odds ratios adjusted for age, body mass index, education and female hormone medications. The incidence of varicose veins did not increase as consistently, being 17.3 (per 1,000 person-years) in those with no births, 15.7 in those with one, 15.6 in those with two and 30.2 in those with three or more births. Adjusted incidence odds ratio, IOR was 2.0 (95% confidence interval, CI: 1.0–3.9) in the highest parity group compared to the nulliparous group.

In the incidence study there were 596 women who had used oral contraceptive pills (Table 3). Most of them were in the youngest cohort. More than half of the users (58.7%) had been taking contraceptive pills for at most three years, whereas the proportion of those who been taking contraceptive pills for at least ten years was 14.3%. The proportion of those who had used oral contraceptive pills was greater (52.0%) in the incidence study than in the prevalence study (46.2%). The prevalence and incidence of varicose veins was lower among those who had used oral contraceptives, but the adjusted odds ratio was not statistically significant for prevalence or incidence (Table 4).

Table 3. Number (and proportion in per cent) of individuals in the incidence study by confounding factors and risk factors.

Variable		Incidence study population (N=2400)			
		Men (N=1253)		Women (N=1147)	
		n	%	n	%
Confounding factor					
Age	40–45	571	45.6	570	49.7
	50–55	380	30.3	338	29.5
	60–65	302	24.1	239	20.8
Education*	Higher	423	33.8	463	40.4
	Lower	777	62.0	643	56.1
	Other	20	1.6	20	1.7
	Missing	33	2.6	21	1.8
BMI**	Lower	544	43.4	700	61.0
	Higher	698	55.7	431	37.6
	Missing	11	0.9	16	1.4
Risk factor					
Number of births	0	-	-	217	18.9
	1	-	-	292	25.5
	2	-	-	413	36.0
	≥3	-	-	214	18.7
	Missing	-	-	11	1.0
OC use	No	-	-	523	45.6
	Yes	-	-	596	52.0
	Missing	-	-	28	2.4
HRT use	No	-	-	1019	88.8
	Yes	-	-	128	11.2
	Missing	-	-	0	0
Daily bread consumption	0–2	163	13.0	196	17.1
	3–4	399	31.8	497	43.3
	>4	681	54.3	450	39.2
	Missing	10	0.8	4	0.3
Weekly meat meals	0–2	150	12.0	254	22.1
	3–6	857	68.4	763	66.5
	>6	224	17.9	107	9.3
	Missing	22	1.8	23	2.0
Weekly alcohol consumption	No	367	29.3	669	58.3
	Yes	879	70.2	478	41.7
	Missing	7	0.6	0	0
Smoking (> 1 year)	No	443	35.4	746	65.0
	Yes	793	63.3	390	34.0
	Missing	17	1.4	11	1.0
Family history	No	544	43.3	519	45.2
	Yes	429	34.2	507	44.2
	Uncertain	273	21.8	121	10.5
	Missing	7	0.6	0	0

*Education: higher (university, college and high school) or lower (comprehensive school and vocational school)

**Body mass index: lower (<25kg/m^2) or higher (≥25kg/m^2)

Table 4. Number of women (n) in prevalence and incidence studies, prevalent (%) and incident (n) cases of varicose veins, incidence rate (per 1,000 person-years) and adjusted* odds ratios with 95% confidence intervals (CI) for the prevalence (OR) and the incidence (IOR) of varicose veins by parity and hormone medications.

Risk factor	Prevalence of varicose veins			Incidence of varicose veins			
	n (N=2948)	Cases (%)	Adj*OR (CI)	n (N=1147)	Cases (n)	Rate	Adj* IOR (CI)
Births							
0	502	33.5	1	217	18	17.3	1
1	705	39.7	1.3 (1.0–1.7)	292	22	15.7	1.0 (0.5–2.0)
2	1050	44.9	1.6 (1.2–2.1)	413	31	15.6	0.9 (0.5–1.8)
≥3	672	54.6	2.0 (1.5–2.7)	214	30	30.2	2.0 (1.0–3.9)
OC use							
No	1540	48.1	1	523	49	19.7	1
Yes	1362	39.2	0.9 (0.8-1.1)	596	50	17.5	0.9 (0.6–1.5)
HRT use							
No	2253	42.1	1	1019	92	18.9	1
Yes	379	54.1	1.3 (1.0–1.7)	128	13	21.4	1.0 (0.5–1.9)

*=adjusted for sex, age, BMI, education and the other variables in the table

At the beginning of the study 12.9% of the women reported using hormone replacement therapy. In those initially free from varicose veins 11.2% reported the use of hormone replacement medication and the majority of them were from the 50-year-old cohort. Prevalence of varicose veins was higher in users (54.1%) than in non-users (42.1%), with adjusted OR 1.3 (95% CI: 1.0–1.7) (Table 4). The incidence rate was also higher (21.4) in those taking the medication than among non-users (18.9). However, after adjusting for confounding factors the effect disappeared, IOR was exactly 1.0 with 95% confidence interval from 0.5 to 1.9.

5.3 Dietary factors, alcohol consumption, smoking and the occurrence of varicose veins (II)

Subjects consuming three to four slices of bread per day had a slightly higher prevalence of varicose veins (34.9%) than the other groups, 0–2 and >4 slices of bread (32.9% and 33.2%) (Table 5). In the incidence study the highest incidence of varicose veins (16.2 per 1,000 person-years) was in the group reporting the smallest bread consumption. There were no statistically significant differences in adjusted odds ratios of prevalence or incidence of varicose veins between different categories of bread consumption.

The prevalence of varicose veins in the categories of the number of meat meals decreased from 39.0% in those having none to two meals of meat per week to 27.8% in those having more than six meals of meat a week. Incidence of varicose veins also decreased in the same categories of meat meals from 19.7 (per 1,000 person-years) to 8.6. The trend was confirmed by adjusted IOR from 1 to 0.5 (95% CI: 0.3–1.1), but did not reach statistical significance. (Table 5) When both sexes were analyzed separately the trend was seen in women, IOR from 1 to 0.4 (95% CI: 0.2–0.99), but not in men, IOR from 1 to 0.98 (95% CI: 0.3–2.9).

Table 5. Number of subjects (n) in prevalence and incidence studies, prevalent (%) and incident (n) cases of varicose veins, incidence rate (per 1,000 person-years) and adjusted* odds ratios with 95% confidence intervals (CI) for the prevalence (OR) and the incidence (IOR) of varicose veins by lifestyle factors.

Risk factor	Prevalence of varicose veins			Incidence of varicose veins			
	n (N=4632)	Cases (%)	Adj*OR (CI) (N=3644)	n (N=2400)	Cases (n)	Rate	Adj* IOR (CI) (N=2202)
Daily bread (slices)							
0–2	699	32.9	1	359	28	16.2	1
3–4	1715	34.9	1.0 (0.8–1.3)	896	56	12.9	0.9 (0.5–1.4)
>4	2182	33.2	1.1 (0.9–1.4)	1131	72	13.2	1.1 (0.7–1.8)
Weekly meat meals							
0–2	869	39.0	1	404	38	19.7	1
3–6	3096	34.0	1.0 (0.8–1.2)	1620	102	13.0	0.7 (0.5–1.1)
>6	579	27.8	0.9 (0.7–1.2)	331	14	8.6	0.5 (0.3–1.1)
Weekly alcohol consumption							
No	2210	39.3	1	1036	64	12.7	1
Yes	2398	28.6	1.1 (0.9–1.2)	1357	93	14.2	1.5 (1.05–2.3)
Smoking > 1 year							
No	2395	38.8	1	1189	76	13.2	1
Yes	2185	28.5	1.0 (0.9–1.2)	1183	77	13.5	1.3 (0.9–1.8)

*=adjusted for sex, age, BMI, education and the other variables in the table

58.3% of the incidence study population reported weekly alcohol consumption. The prevalence of varicose veins in those consuming alcohol weekly erroneously indicated a protective effect (28.6% vs. 39.3%), whereas the findings in the follow-up study showed quite the opposite (Table 5). Adjusted IOR was 1.5 (95% CI: 1.05–2.3) in those drinking alcohol compared to those abstaining from it. The result was statistically significant only in women IOR 1.6 (95% CI: 1.02–2.5), but not in men IOR 1.4 (95% CI: 0.7–2.8) when the genders were analyzed separately.

Half of the incidence study population reported ever having smoked over a year (Table 3). They had slightly higher incidence of varicose veins than non-smokers, with IOR 1.3 (95% CI: 0.9–1.8) (Table 5). However, the difference was not statistically significant. A stronger effect was seen in further analysis in those smokers who reported the amount of smoking at least 15 cigarettes/cigars/pipefuls a day (n=466), IOR 1.8 (95% CI: 1.1–2.8) compared to non-smokers. The prevalence of varicose veins in smokers (28.5%) was lower than in non-smokers (38.8%) indicating the opposite result as was now found in the follow-up (Table 5).

5.4 Family history and the occurrence of varicose veins (III, IV)

The information on family history of varicose veins was missing from only 15 men and 7 women at entry. The numbers of subjects responding “do not know” about family history were greater among men than among women both at entry (24.0% vs. 13.6%) and among those followed up (21.8% vs. 10.5%). The prevalence of varicose veins was 47.5% in those reporting positive and 15.0 % in those with negative family history of varicose veins (Table 6). According to prevalence, family history indicated a high risk of varicose veins. Age and body mass index adjusted OR was 5.3 (95% CI: 4.5–6.3). The incidence of varicose veins in those with positive family history was 16.5 per 1,000 person-years, 10.0 in men and 22.1 in women. Adjusted IOR was 1.6 (95% CI: 1.1–2.3), 1.4 (95% CI: 0.7–2.6) in men and 1.8 (95% CI: 1.1–2.8) in women.

The smaller multi-adjusted odds ratio of 1.6 based on the follow-up compared to the 5.3 based on the prevalence is an indication of misclassification due to recall bias and other factors. Therefore we further studied the potential of misclassification to be differential by comparing the effect of changes in the subject’s varicose veins status on the information on family history. In the whole population odds ratio was 0.63, i.e. prevalence of positive family history became more uncommon during follow-up (Table 7). However, it varied from 0.14 (if a subject’s own varicose veins disappeared for some reason) to 6.00 (if a subject developed varicose veins during follow-up).

Table 6. Number of subjects (n) in prevalence and incidence studies, prevalent (%) and incident (n) cases of varicose veins and adjusted* odds ratios with 95% confidence intervals (CI) for prevalence (OR) and incidence (IOR) of varicose veins by family history.

Risk factor		Prevalence of varicose veins			Incidence of varicose veins			
		n	Cases (%)	Adj*OR (CI)	n	Cases (n)	Rate/ 1000	Adj* IOR (CI)
Family history								
All	No	1550	15.0	1	1063	54	10.4	1
	Yes	2254	47.5	5.3 (4.5–6.3)	936	74	16.5	1.6 (1.1–2.3)
	Uncertain	809	31.6	3.0 (2.4–3.8)	394	29	15.3	1.6 (1.0–2.6)
Men	No	719	6.7	1	544	20	7.5	1
	Yes	766	30.3	6.6 (4.7–9.3)	429	21	10.0	1.4 (0.7–2.6)
	Uncertain	461	19.3	3.4 (2.3–5.0)	273	11	8.2	1.0 (0.4–2.1)
Women	No	831	22.3	1	519	34	13.5	1
	Yes	1488	56.4	4.9 (4.0–6.0)	507	53	22.1	1.8 (1.1–2.8)
	Uncertain	348	48.0	3.0 (2.2–3.9)	121	18	32.1	2.3 (1.2–4.4)

*= adjusted for age and body mass index (BMI as a dichotomous variable, with 25 kg/m^2 as a cut-off point), in all-group also with sex

Table 7. Number of subjects (n) by self-reported own status of varicose veins at entry and at the end of follow-up (O (·,·)) and by family history of varicose veins at entry and at the end of follow-up (F (·,·)) with kappa coefficients of consistency and odds ratios of family history by own status of varicose veins.

	n	F(–,–)	F(–,+)	F(+,–)	F(+,+)	Kappa	95% CI*	OR	95% CI*
O(–,–)	1380	611	53	103	613	0.77	0.74–0.81	0.51	0.41–0.61
O(–,+)	101	21	12	2	66	0.66	0.50–0.82	6.00	2.01–47.8
O(+,–)	56	15	1	7	33	0.69	0.49–0.88	0.14	0.01–0.58
O(+,+)	909	97	25	33	754	0.73	0.67–0.80	0.76	0.57–0.89
Total	2446	744	91	145	1466	0.79	0.76–0.81	0.63	0.54–0.71

The incidence rate of varicose veins in subjects with no varicose veins at entry varied between the four family history categories (F (·,·)). It was 4.1 (95% CI: 2.1–7.1) in those who reported positive family history only at the end of follow-up F(–,+) and lowest 0.4 (95% CI: 0.1–1.4) in those reporting positive family history only at entry F(+,–). Incidence rate was 0.7 (95% CI: 0.4–1.0) in F(–,–) group and 2.0 (95% CI: 1.6–2.6) in F(+,+) group.

6. DISCUSSION

6.1 Study population and methods

The study population was a representative sample of Finns in middle and late adulthood living in a middle-sized Finnish city. Altogether the response rates were unusually high and much higher than in most postal questionnaire studies published in medical journals (approximately 60%) (Asch et al. 1997). The response rates were higher among women (86% in the first and 92% in the second questionnaire) than among men (75% and 83% respectively) and higher in the older cohorts compared to the youngest ones (Figure 2). Previous research has demonstrated that written reminders (Asch et al. 1997, Edwards et al. 2002, Ronckers et al. 2004) and monetary incentives (Church 1993, Edwards et al. 2002) increase response rates, and the former was used in the present study. Other explanations for the high response rates are that the questionnaire was only four pages long and the material was collected in the 1990s. It is known that response to a shorter questionnaire is more likely than to a longer one (Edwards et al. 2002, Ronckers et al. 2004) and that participation in surveys in general has declined in recent decades (Morton et al. 2006).

However, the response rates in men were lower than those in women and lowest in the youngest cohort in both sexes (Figure 2). Common reasons for non-response are a feeling of lack of personal benefit from responding (Bakke et al. 1990) and a negative attitude to the health care system (Janzon et al. 1986). A low response rate in a questionnaire study may increase the risk of selection bias (Rothman and Greenland 1998). A higher response rate in men would have resulted in narrower confidence intervals and better statistical power. Among women the evidence of the selection bias is the difference in varicose veins status in those among follow-up (42.7%) compared to those lost from follow-up (33.0%). The response rate in women was very good and the proportion of non-respondents small, which has no substantial effect on the outcomes of the study, however.

Respondents also differed from non-respondents according to lifestyle factors. According to earlier studies, it is a common finding that a higher proportion of non-respondents are smokers than of respondents (Kelsey et al. 1986), as indeed in our study. It is assumed that non-participation may affect the generalizability of the results (Kelsey et al. 1986), which means that the occurrence of varicose veins in our study may be slightly lower than in the entire population invited to participate.

The terminology used to define and classify varicose veins in subjects is not consistent. Specifically the comparison with earlier studies is challenging due to the lack of precision in diagnosis before the CEAP classification. Several overlapping clinical manifestations of the same disease process have been defined as "varicose veins". In this study we used the definition proposed by Arnoldi (1957), which concurs with clinical class 2 in the CEAP classification, the latest consensus statement on classification of chronic venous disorders (Eklöf et al. 2004). In the sub-sample study the specificity (0.92) and sensitivity (0.93) of the self-reported diagnosis was fairly good but less so in those with positive family history (0.83 and 0.91 respectively). The differences between respondents initially raised the question about bias in self-reported family history, which was then studied further as one aim of the dissertation and discussed in more detailed in Chapter 5.4.

We collected the information on the study population by self-administered postal questionnaires, which are prone to biased information. The responses may be affected by anyone around, such as other family members. Also, complicated questions are not always well understood by the respondent. (Kelsey et al. 1986)

Earlier studies have also compared the self-reporting of varicose veins to clinical examination of varicose veins and the results have varied widely. In an English study the sensitivity (76%) and specificity (86%) were somewhat less than in our study (Franks et al. 1992). In an Italian study on elderly people there was a good correspondence between responses and clinical findings (29.6% reported vs. 27.4% positive in the clinical examination) (Canonico et al. 1998). Poorer results were reported from a study in Israel; the sensitivity of the interview data was only 47% in men and 67% in women, hence the specificity was 95% in men and 85% in women (Abramson et al. 1981). In the study by Weddell (1969) of those with varicose veins, 52% of the observations by the rest of the family proved to be correct and 48% did not, while in those without varicose veins 93% were correct and 7% were not. In conclusion, compared to earlier studies misclassification of varicose veins in the present study was likely to be low.

There are also some weaknesses in questionnaires themselves. When potential risk factors are studied, it is important to classify subjects already at entry into those who are exposed and to those who are not. Here, education and the lifetime use of oral contraceptive pills were only elicited in 1994. However, it may be assumed that education has changed little in middle-aged population during follow-up or that there were not many new contraceptive users after 1989 among 40-year-olds not to mention women in older cohorts. Therefore information on education and the use of oral contraceptive pills would have been essentially the same if already elicited at study entry in 1989 and consequently did not affect the number of subjects exposed.

We used body mass index >25kg/m^2 as an indicator of overweight. It is known that under-reporting of weight (Villanueva 2001, Gorber et al. 2007) and over-reporting of height (Gorber et al. 2007) are common. In Finland overweight also

increases with age in working population (Lahti-Koski et al. 2000). In our study 58% of the men and 45% of the women were overweight at entry according to self-reported weight and height. There is some under-reporting if the proportions are compared to the National FINRISK Study in Finland in 1987, where the subjects were measured by trained nurses. According to this research body mass index was ≥25kg/m^2 in 64% of men aged 35–44 years and 74% of men aged 45–54 years. The corresponding percentages were 41 and 62 in women (Lahti-Koski et al. 2000). There was some variation in body mass index between the two questionnaires; the category was changed for 14% of the men and 15% of the women during the follow-up and three-quarters of them from the lower category of body mass index to the higher one in both genders. We used body mass index as a binary variable with 25kg/m^2 as a cut-off point. Multivariate analyses were repeated with changing the classification of body mass index (e.g. BMI classified in three categories or 30kg/m^2 as a cut-off point), but it did not significantly change the results.

Furthermore, we did not elicit passive smoking, which may have increased the number of those exposed to the effects of smoking, especially in women. However, there are no studies on the effects of passive smoking on varicose veins, i.e. it is an open question whether there are any effects at all. With regard to alcohol consumption, it is commonly known that the consumption of alcohol is underreported (Feunekes et al. 1999). However, we classified subjects only crudely into weekly users and non-users of alcohol, thus this hardly biased the results in our study. Also, the use of a standardized food frequency questionnaire would have been more valid for collecting data on diet. As diet was not the main interest of the Tampere Varicose Vein Study, the crude and limited information related to all possible risk indicators of varicose veins was deemed sufficient at the planning phase of our study. We also intended to keep the requested data set small in order to achieve the highest possible response rate. The effect of crude questioning is to reduce the estimate of effect. Therefore, it is unlikely that the result on meat can be accounted for bias from this source.

We studied both the prevalence and incidence of varicose veins by different potential risk factors. Prevalence as a measure of disease occurrence gives a good picture of the total burden of the condition in a population, but for etiological purposes incidence is better. In a longitudinal study with multiple assessment time-points the risk factor (potential cause) can be better controlled and demonstrated to precede the effect. Therefore, the main emphasis in the results and in the discussion is on the incidences found by the five-year follow-up design.

A methodological weakness is our assessment of varicose veins at only two time-points during follow-up, at entry and at the end of the five-year period, thus the exact time point for the appearance of varicose veins is not known. We assumed that new varicose veins occurred on average at the midpoint of the follow-up period, thus the person-years for incident cases were approximations. This may have caused some inaccuracy in the estimates of incidence. However, the effect of this should be equal

on both sides of the selected mid-point. Also, because of the crude classification of the confounding factors in the multivariate analysis, there may be some residual confounding.

6.2 Results

6.2.1 Occurrence of varicose veins

There is a note worthy variation worldwide in the reports of the occurrence of varicose veins. Only three studies have estimated the incidence of varicose veins in developed countries and none in developing countries. In Finland, the incidence of varicose veins, 13.5 per 1,000 person-years (Mäkivaara et al. 2004) is at the medium level compared to the longitudinal follow-up studies in Italy (Cesarone et al. 2002) and the USA (Brand et al. 1988).

The prevalence estimates from Finland (18% in men and 42% in women in the Tampere Varicose Vein Study, and 7% in men and 25% in women in the national health survey) are also on average level among other industrialized countries. The highest estimates in Europe have been reported in Italy (Chiesa et al. 2007). Much lower rates have been reported from developing countries, but some facts must be kept in mind when comparing the results with those from developed countries: Most of the literature is old, for example all of the studies from Africa were completed in the 1960s and 1970s. At that time, life expectancy there was even lower than nowadays and is still much lower than in western countries. Typically, the reported mean ages for study populations are also lower. In the case of varicose veins, which occur throughout adulthood, the cumulative prevalence is lower in younger population. However, even today the situation may have changed because of the increased life expectancy and changes in lifestyle in developing countries, too.

There are two population-based studies from Asia. Based on the results the prevalence of varicose veins is 14% in adult population of the Kingdom of Saudi Arabia (Bawakid et al. 2005) and 21% in the population (mainly immigrants) of western Jerusalem (Abramson et al. 1981). The few other studies from Asia are from selected study populations, e.g. occupational groups with widely disparate results. In future, especially in the world's most densely populated continent, well-designed population-based studies are needed to ascertain the magnitude of the problem.

6.2.2 Female hormones and varicose veins

In the present study, three or more births doubled the risk of varicose veins compared to that of nulliparous women. Instead, the incidence of varicose veins was not increased in women with one, or in women with two births compared to women who have not given birth. It was not self-evident that there would be a higher incidence in multiparous (≥3 births) middle-aged women, who had had their pregnancies years before. Our result is almost similar to that of the Framingham Study, where women (aged 40–89) with two or more pregnancies had a higher incidence of varicose veins compared to those with one or no pregnancies, but without statistical significance (Brand et al. 1988).

The prevalence of varicose veins increased with increasing number of pregnancies, and one pregnancy was already associated with a significantly higher risk (OR 1.3). Higher risk in those with at least one pregnancy has also been reported in elderly populations in Italy (aged 65+) (Canonico et al. 1998) and in Turkey (aged 60+) (Komsuoglu et al. 1994), and in a younger study population (aged 18 years and older) in France (Carpentier et al. 2004). There are also a couple of studies reporting parity not to be associated with varicose veins (Weddell 1969, Coon et al. 1973, Guberan et al. 1973) or trunk varices (Lee et al. 1999).

The estimates of the risk in women with one or two births differed between prevalence and incidence design in our study. One explanation could be that a genetic factor may contribute more in young age to the development of varicose veins. Subjects with varicose veins at entry were only included in the prevalence analysis. Nor were the women who only contracted the disease in middle age in spite of one or two births, so susceptible in middle age. The threshold for significantly increased risk was three births.

Pregnancy is associated with a number of physiological changes which may contribute to the development of varicose veins. The mechanisms are unclear, but probably more than one factor is involved. The hormonal changes are dramatic, in which estradiol and progesterone play a major role with levels elevated 10-fold compared to non-pregnant state. More estrogen (Mashiah. et al. 1999, Knaapen et al. 2005) and progesterone receptors have been found in the varicose part of saphenous vein (Mashiah et al. 1999), which favors the idea of hormone influence on varicose veins. The major increase in estradiol in serum occurs within the first 16 gestational weeks followed by a further moderate increase by term, whereas the progesterone level increases more gradually (O'Leary et al. 1991). Recent studies have also reported relaxin to have vasodilatory potential and possibly also to promote angiogenesis. In pregnancy it is secreted by the corpus luteum, reaching the highest

level in the first trimester and having the effect of softening the birth canal. (Dschietzig et al. 2006)

Early in pregnancy there is a significant increase in plasma volume (Bernstein et al. 2001) and blood flow (Fawer et al. 1978), also a significant dilatation of the veins of lower extremities either in women with normal (Cordts et al. 1996, Pemble 2007) or varicose veins (Sparey et al. 1999). However, the results of the above-mentioned studies were inconsistent with respect to the reversibility of the pregnancy-induced dilatation. The latest study in primipara women (n=39 gravida, n=69 nulliparous controls) found that the reversal of the dilation after delivery is not complete (Pemble 2007) as was earlier assumed on the basis of studies with smaller sample sizes (n=8 and n=11) (Cordts et al. 1996, Sparey et al. 1999). This new finding indicates permanent structural changes in the veins, which may deteriorate in subsequent pregnancies and explain the increased risk of developing varicose veins in multiparous women (Pemble 2007).

In the second and third trimesters the enlarging gravid uterus may compress the inferior vena cava and iliac veins, reducing venous return from the lower extremities, which increases the venous pressure and could contribute to the development of varicose veins during pregnancy (Arnoldi 1957). However, that theory disagrees with the understanding that most varicose veins already appear in the first trimester (Arnoldi 1957, Dodd and Cockett 1976, Schadeck and Vin 1984).

To conclude, the hormonal changes and the increased blood volume and flow, concurrently with the appearance of varicose veins in the early stages of pregnancy suggests their involvement in the development of varicose veins. The measurable changes during pregnancy are mostly temporary, but at least small structural changes in the vein wall could be permanent, leading to the subsequent development of varicose veins. The present study showed that middle-aged women who have had at least three pregnancies have a two-fold risk of varicose veins compared to nulliparous women.

One aim of the present study was to assess if the same hormones in the form of contraceptive pills or hormone replacement therapy have an effect on the incidence of varicose veins. Estrogen and progesterone (or their derivatives), or progesterone alone, are used in contraceptive pills, whereas postmenopausal hormone therapy consists of estrogen alone, or in combination with progesterone (if a woman has not had a hysterectomy). Half of the women (52%) in the follow-up had used contraceptive pills and 11% hormone replacement therapy. Unfortunately, we did not have the opportunity to ascertain the type of contraceptive pills or hormone replacement therapy used.

Studies on hormonal medications and varicose veins are rare. Most of the few studies on oral contraceptive use and varicose veins have found no association. Our results concur with these. Only a study of 500 telangiectatic or varicose veins patients

and 500 healthy controls implicated oral contraceptive use as a predisposing factor to the development of telangiectatic and varicose veins (Sadick 1992).

We did not find a significant difference in the incidence of varicose veins between the users and non-users of hormone replacement therapy. The number of hormone replacement users in our study population was quite small, partly due to the age-cohorts included. The average age at menopause is 51 years (Greendale et al. 1999), and two cohorts were younger at the beginning of the follow-up. However, there are no previous longitudinal studies against which to compare our results.

In the present study the prevalence of varicose veins was somewhat increased in women who had used hormone replacement therapy. A parallel result was reported in a cross-sectional study from Finland (Sisto et al. 1995), where a significantly higher prevalence was observed in women aged 50 years and over. Similarly, a Saudi-Arabian study performed a higher risk of varicose veins among users of hormone replacement therapy compared to non-users (OR 1.5 (95% CI: 1.2–1.9)), but they included subjects with a wider spectrum of venous insufficiency (CEAP 1–4) in their study. The relationship was opposite in the Edinburgh Vein Study, where subjects using hormone replacement therapy had a decreased risk of trunk varices, with odds ratio of 0.48 (95% CI: 0.25–0.91) (Lee et al. 2003).

If there is an association between varicose veins and female hormones, the number of lifetime cycles of menstruation could be meaningful. We could then assume an increase in the prevalence of varicose veins among women with a long duration of menstrual life, that is, an early age of menarche and a late onset of menopause. Only one of the few studies has supported this conjecture. In the Framingham Study, women with varicose veins were older at menopause (Brand et al. 1988). If Brand et al. (1988) are right, and menopause has an effect on varicose veins, menopause should have been considered a confounding factor. In this respect, due to lack of information on menopause, it is possible that no potential association was found.

The information on menopause would also have made it possible to study the potential association in detail, since the latest data on an association between hormone replacement therapy and cardiovascular disease have suggested the timing of the treatment and the type of progestin used to underly the contradictory statements on the effects of hormone replacement therapy. There are suggestions that should hormone replacement medication be used in the early postmenopausal years, the effect on vascular wall due to the inhibition of atherosclerosis may be protective, whereas in late menopause adverse effects may develop. (Gungor et al. 2009) However, the effects of hormone replacement therapy on the vein walls could be different from the effects on arteries.

In conclusion, there was no association between external female hormones and varicose veins in our study. Further studies are needed to consider the most recent information from the arterial side on the study design. However, the considerable

difference in the occurrence of varicose veins between sexes could not be explained by female hormones alone.

6.2.3 Dietary factors, alcohol consumption, smoking and varicose veins

There are some epidemiologic studies on the possible association between lifestyle factors and varicose veins. The lifestyle factors included in our study were daily bread consumption, weekly meat consumption, alcohol consumption and smoking (of cigarettes, cigars or pipes).

We studied the association between varicose veins and dietary fiber by asking daily bread use, and found no association. In the Edinburgh Vein Study fiber intake was assessed with a specific questionnaire, and likewise found no association between trunk varices and dietary fiber (Lee et al. 2003). Earlier speculations on the role of diet in the etiology of varicose veins have been raised in order to explain the differences in the occurrence of varicose veins between developing and developed countries (Cleave 1959, Dodd 1964, Burkitt 1972). Western diet has been blamed for deficiency in fiber. Subsequent constipation and straining at stool could increase intra-abdominal pressure and valvular incompetence and as such increase the risk for varicose veins. However, the four studies have not succeeded in confirming the association between varicose veins and constipation (Mekky et al. 1969, Abramson et al.1981, Canonico et al.1998, Criqui et al. 2007).

The present study also hypothesized the intake of meat in the etiology of varicose veins. Meat is the main source of protein in a Finnish diet providing one third of the daily protein intake (Paturi et al. 2008). Interestingly, the results implied an inverse association between the frequency of meat intake and varicose veins, but it was statistically significant only in women. There was a trend-like dose-response gradient between meat consumption and varicose veins. To the best of our knowledge, one study has investigated the association between varicose veins and protein intake, but reported no relationship (Ducimetiere et al. 1981).

It is difficult to put an accurate interpretation on this finding. We adjusted for age, body mass index and education, but lifestyle is dependent on several other background characteristics, too. These factors could be the true protective factors behind abundant meat consumption.

The three existing studies on alcohol consumption and varicose veins (Carpentier et al. 2004, Scott et al. 2004) or venous insufficiency (Gourgou et al. 2002) have analyzed alcohol consumption as a bivariate trait, but the cut-off points have been different. The lowest limit was >10g per week in the French study (Carpentier et al. 2004) and this classification was closest to the classification in our study. The two others were ≥2 drinks per day (Scott et al. 2004) and ≥80g per day in men and ≥40g

per day in women (Gourgou et al. 2002). In any case, none of these cross-sectional studies found any association between alcohol consumption and varicose veins.

In the present study we were able to show that weekly alcohol consumption contributes to the incidence of varicose veins. The risk in those drinking alcohol weekly was 1.5-fold compared to non-drinkers (or those drinking alcohol occasionally). However, the finding was statistically significant only in women. It is known that alcohol consumption affects the vascular system (Bau et al. 2005, Bau et al. 2007) but in which way and on exactly which part is still uncertain.

The crude, non-adjusted rates even indicated a protective effect of alcohol consumption. Studies based solely on prevalence estimates showed no association between varicose veins and alcohol consumption. The fact that there is a difference between the results of incidence and prevalence studies emphasizes the importance of adequate study methods.

By far the most studied lifestyle factor is smoking, and with inconsistent results (Brand et al. 1988, Sisto et al. 1995, Lee et al. 2003, Kroeger et al. 2004, Scott et al. 2004). The only existing follow-up study on smoking and varicose veins detected an elevated risk in current smokers (RR 1.3) (Scott et al. 2004). We agree with that result. In our study, those who had ever smoked at least over a year had IOR 1.3 compared to non-smokers, however, the result was not statistically significant. Among heavy smokers (≥15 cigarettes a day) the harmful effect of smoking on varicose veins was clearer. The risk of varicose veins in those increased compared to non-smokers, IOR 1.8, with statistical significance.

A case-control study in France reported a dose-effect relation of tobacco smoking on lower limb venous insufficiency to be significantly associated with adjusted odds ratio from 1.4 (95% CI: 0.9–2.2) for 10-19 cigarettes/day to 2.1 (95% CI: 1.4–3.2) for ≥20 cigarettes/day in men and from odds ratio 1.8 (95% CI: 1.3–2.3) to 2.4 (95% CI: 1.7–3.4) in women, respectively (Gourgou et al. 2002).

The mechanisms responsible for the harmful effects of tobacco on the venous system are not exactly known. However, studies on arteries have published a strong association between smoking and peripheral arterial disease (Willigendael et al. 2004, Agarwal 2009). The cross-sectional results did not show an increased risk of smoking on varicose veins. Instead, the prevalence of varicose veins was higher in non-smokers (39%) compared to smokers (29%).

In the present study alcohol consumption and small amount of meat in diet increased the risk of varicose veins in women, while smoking seemed to be a risk factor in both men and women. The associations were found in the follow-up design, and differed from the prevalence results, particularly in alcohol consumption and smoking. Follow-up design is more credible for studying risk factors. The data of the risk factors are observed at entry and the disease is detected in subjects originally free of it during the subsequent follow-up, hence information on exposure is less biased. In

addition, only longitudinal design can assess a temporal relationship, which is essential in assessing causality and in detecting risk factors.

6.2.4 Heredity and varicose veins

Positive family history is considered one of the main risk factors for varicose veins based on cross-sectional studies with prevalence estimates (Komsuoglu et al. 1994, Lee et al. 2003, Carpentier et al. 2004, Kroeger et al. 2004), but the estimates of the magnitude of the risk vary a lot in published data. The few studies on genes support a genetic influence on venous function (Brinsuk et al. 2004) and on the etiology of varicose veins (Ng et al. 2005). However, positive family history does not automatically mean a genetic cause. The family usually shares the same environment and lifestyle. They may even have the same occupations and other ways of life exposing them to varicose veins, which could lead to another kind of family-linked cause.

Most studies have relied on the information obtained from study subjects, not consulting or examining relatives themselves. Neither did we have the opportunity to examine the relatives. The validity of the self-reported information on relatives is open to question. A person who has varicose veins is more likely to know whether he or she has a relative who also suffers from the condition. However, in Finland the traditional lifestyle includes sauna bathing, which makes direct observation of family members acceptable and easy. Therefore, Finns may know the family history of varicose veins slightly better than people in many other countries.

We had a unique opportunity to assess familial predisposition based on a follow-up design. Only those who did not have varicose veins at entry were included in the incidence study. The family history was elicited at entry, so it was not affected by the respondent's own varicose vein status during follow-up. If at least one of the first-degree relatives from an originally healthy family was reported to have varicose veins at the end of follow-up it was enough to change the classification from a negative family history to a positive one. On the other hand, a new affected relative did not cause any change in the classification in subjects whose family history was already considered positive at entry. The number of men uncertain about family history was greater than the number of uncertain women, and the IOR of incidence was also lower in uncertain men (1.0) than in uncertain women (2.3). Women could be more interested in health-related factors in the family, and that could explain the greater uncertainty of men, whereas the lower incidence of varicose veins in uncertain men compared to uncertain women is more difficult to explain. One explanation could be that uncertain women already had varicose veins at entry, but they did not know it – neither did they know of a family history of varicose veins, but after completing up

the questionnaire they became interested in the subject and noticed their own varicose veins, too. Nor could the possibility of chance variation be ruled out.

We found the risk in those with positive family history to be 1.6-fold compared to those with negative family history. When both genders were analyzed separately, the odds ratio was 1.8 in women and 1.4 in men, but without statistical significance. There are no earlier longitudinal results to compare our findings with. The risk estimates are at the same level as cross-sectional results in the Edinburgh Vein Study (Lee et al. 2003). They reported an adjusted odds ratio of 1.5 in men and 2.2 in women. Most other cross-sectional studies have reported much higher estimates of the risk (Gourgou et al. 2002, Carpentier et al. 2004, Kroeger et al. 2004).

The difference warranted us to study this issue further in order to explain at least some of the difference. We studied potential misclassification bias by comparing subjects' own varicose vein status or changes in it with the self-reported family history of the whole study population in the two questionnaires. We also included those who had varicose veins at entry. We found the consistency of family history of varicose veins to be higher if subjects' own self-reported status of varicose veins was consistent and less if the self-reported status of varicose veins was different in the questionnaires. For example, the highest odds ratio (6.00) was observed in those who developed varicose veins during follow-up. The maximal ratio of odds ratios for remembering family history was about 40 (6.00 versus 0.14), indicating substantial recall bias.

On the other hand, the incidence rate of varicose veins varied from 0.4 to 4.1 (per 100 person-years) depending on how the subject recalled the family history. The variation is difficult to explain by a real effect, it is rather explained by observer bias. A subject becomes more sensitive to his/her own varicose veins if there is a strong family predisposition.

An overall decrease in the prevalence of family history between the two questionnaires was also observed. This may be because of bias or it may be true: The relatives with varicose veins may have died during follow-up, but such selection is unlikely because varicose veins as such are not lethal. On the other hand, there is a chance that subjects want to forget their varicose veins after treatment, as well as the varicose veins in the rest of the family. It is more likely that new varicose veins appeared during the follow-up in the relatives, too, and if anything, the odds ratios would be >1.

An explanation for the difference in results between cross-sectional and follow-up studies is that subjects with strong genetic predisposition to varicose veins may have acquired them at a younger age. In that case, in our study design they were included in the cross-sectional population, where they increased the prevalence estimate and were excluded from follow-up. However, in the eight-year Bochum Study on pupils aged 10–12 years at entry, only a weak association between family history and occurrence of varicose veins was found (Schultz-Ehrenburg et al. 1992).

Overall, family history is a risk factor or a predictor of varicose veins, particularly in women. According to our results the risk is not as high as earlier assumed in the literature. Differential misclassification bias in ascertainment can explain part of the very high risk estimates in cross-sectional studies.

7. SUMMARY AND CONCLUSIONS

The etiology of varicose veins is unclear. The present knowledge of risk factors of varicose veins is mainly based on cross-sectional studies with prevalence estimates. Cross-sectional studies lack follow-up, causing difficulty in assessing the temporal relationship essential to determining cause and effect. The purpose of the present study was to assess potential risk factors of varicose veins in a five-year follow-up study in middle-aged men and women. Three complete cohorts of 40, 50 and 60 year-old inhabitants of the Finnish city of Tampere were included in the study, of whom 4,903 (71%) responded both at entry and at the end of follow-up. Incidence was studied in subjects free of varicose veins at entry. Prevalence rates were established for purposes of comparison. The potential risk factors studied were parity, oral contraceptives, hormone replacement therapy, diet, alcohol consumption, smoking and family history of varicose veins.

The major findings and conclusions are,

1. The incidence of varicose veins increases significantly in women with three or more births compared to nulliparous women. The risk is twofold. Oral contraceptives or hormone replacement therapy did not have an obvious effect on the incidence of varicose veins in the present study.
2. Alcohol consumption is a risk factor of varicose veins, particularly in women. Smoking is likely to increase the risk of varicose veins, with a stronger effect on heavier smokers. More meat in a diet may protect against varicose veins, especially in women. Dietary fiber intake does not contribute to the occurrence of varicose veins. However, it is possible that there are some other lifestyle or background factors which are the true risk factors or protective factors behind those now reported in our results.
3. The incidence of varicose veins is 1.6-fold in those with positive family history of varicose veins compared to those with negative family history. The risk is not as high as commonly proposed in the literature, consisting mainly of cross-sectional studies with prevalence estimates. There is differential misclassification bias in the ascertainment in cross-sectional studies; among those with varicose veins, they are reported in excess in the family.

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10. APPENDICES

Questionnaires in English and in Finnish in 1989 and 1994.

QUESTIONNAIRE ON CIRCULATORY PROBLEMS IN THE LOWER EXTREMITIES (1989)

SURNAME_____ (FORMER NAME_____)

FORENAME_____ 1.SOCIAL SECURITY NUMBER __ __ __ - ____

2.GENDER [ ] male [ ] female

3.PROFESSION_____ RETIRED [ ]

ADDRESS _____

4.Weight _____ kg Height _____ cm

5.Do any of your closest relatives (parents, grandparents or siblings) have varicose veins?
[ ] NO / [ ] DON'T KNOW
[ ] YES, who _____

6.Have you ever given birth?
[ ] NO / [ ] YES, how many times? ____ , year of the first birth ____.

7.Have you ever used contraceptive pills?
[ ] NO / [ ] YES, how many years? ____.

DIET AND HABITS:

8.What kind of milk do you drink?
[ ] whole milk / [ ] semi-skimmed milk / [ ] skimmed milk /
[ ] other, what kind? _____
How many glasses (2dl) of milk daily? _____ glasses
Do you use (e.g. in food and on bread) [ ] BUTTER /[ ] MARGARINE /[ ] VEGETABLE OIL
[ ] NONE OF THESE
For how many times each week do you eat meals of meat or sausages? _____ times

How many slices of bread do you eat each day? _____ slices

9.Have you ever smoked for longer than one year?

[ ] NEVER
[ ] I HAVE STOPPED SMOKING, at what age did you start ____ and stop ____?
[ ] I NOW SMOKE; -at what age did you start? _____
-do you smoke [ ] cigarettes or [ ] cigars
[ ] pipe
-how much each day? ____ cigarettes/cigars/pipefuls

10.Do you use alcohol?

[ ] NOT AT ALL OR OCCASIONALLY
[ ] YES, how much per week
beer in bottles (1/3 l) ____
wine in bottles (3/4 l) ____ or in glasses (12 cl) ____
spirits in bottles (1/2 l) ____ or in glasses (4 cl) ____

11.Do you get any physical exercise when not at work?
[ ] NOT AT ALL / [ ] OCCASIONALLY / [ ] EACH WEEK / [ ] SEVERAL TIMES A WEEK,
which exercise?_____

12.Which of the following applies to the posture normally assumed in your main (past or present) occupation?

[ ] SITTING WITH LESS THAN ½ HOUR OF STANDING IN A DAY
[ ] MAINLY SITTING, WITH LESS THAN HALF THE WORKING DAY SPENT STANDING
[ ] STANDING FOR OVER HALF OF THE WORKING DAY
[ ] OTHER, what posture _____

IF YOU WORKED ON YOUR FEET, DID YOU WORK IN A STATIC STANDING POSTURE?
[ ] NO
[ ] YES, for how many hours daily (on average)? _____ hours
HOW MANY YEARS? ____ years

PREVIOUS HEALTH:

13.Have you ever suffered conditions requiring medical care?

[ ] NO

[ ] YES, which of these?

-diabetes [ ] NO [ ] YES, since _____
-high blood pressure [ ] NO [ ] YES, since _____
-cardiac infarct [ ] NO [ ] YES, since _____
-angina pectoris [ ] NO [ ] YES, since _____
-insufficiency of the heart [ ] NO [ ] YES, since _____
-pulmonary diseases [ ] NO [ ] YES, which disease _____
-superficial thrombosis in lower extremities [ ] NO [ ] YES, since _____
in which leg? [ ] right/[ ]left
-deep venous thrombosis in lower extremities [ ] NO [ ] YES, since _____
in which leg? [_] right/[_]left
-pulmonary embolism [ ] NO [ ] YES, since _____
-sciatica or other back problems [ ] NO [ ] YES, since _____
-renal diseases [ ] NO [ ] YES, since _____
-fractures in lower extremities [ ] NO [ ] YES, when _____
in which leg? [ ] right/[ ]left
in which part of the leg?_____
-major contusions with prolonged healing [ ] NO [ ] YES, when _____
in lower extremities in which leg? [ ] right/[ ]left
-problems in arterial circulation of the legs [ ] NO [ ] YES, since _____
in which leg? [ ] right/[ ]left
-cerebral circulatory problems [ ] NO [ ] YES, since _____
-ulceration in leg [ ] NO [ ] YES, since _____
in which leg? [ ] right/[ ]left
-other chronic or severe disease, which disease? _____, since _____

14.Have you had a frequent or prolonged experience of the following conditions? (In which leg?)

-sensation of heavy leg(s) in the afternoon [ ] NO [ ] YES -> [ ]RIGHT/[ ]LEFT
-pain or prickly sensation in leg(s) during the daytime [ ] NO [ ] YES -> [ ]RIGHT/[ ]LEFT
-swelling of ankle or leg(s) [ ] NO [ ] YES -> [ ]RIGHT/[ ]LEFT
-swelling of thigh(s) [ ] NO [ ] YES -> [ ]RIGHT/[ ]LEFT
-considerable leg-pain while standing [ ] NO [ ] YES -> [ ]RIGHT/[ ]LEFT
-cold legs [ ] NO [ ] YES -> [ ]RIGHT/[ ]LEFT
-numbness in leg(s) [ ] NO [ ] YES -> [ ]RIGHT/[ ]LEFT
-cramps in leg(s) [ ] NO [ ] YES -> [ ]RIGHT/[ ]LEFT
-permanent change in the color of the skin in ankle or leg [ ] NO [ ] YES -> [ ]RIGHT/[ ]LEFT
-intermittent claudication (explained) [ ] NO [ ] YES -> [ ]RIGHT/[ ]LEFT
-lower-extremity pain while at rest [ ] NO [ ] YES -> [ ]RIGHT/[ ]LEFT
-longstanding ulceration or necrosis in foot or leg [ ] NO [ ] YES -> [ ]RIGHT/[ ]LEFT
-if any of the symptoms have occurred, does it help when you
elevate the legs? [ ] NO [ ] YES
let the legs hang? [ ] NO [ ] YES
-any other symptom?_____
_____

15.Are you on permanent medication?

[ ] NO

[ ] YES, for/medication is

[ ] diabetes
[ ] hypertension
[ ] coronary disease
[ ] arrhythmia
[ ] insufficiency of the heart
[ ] pulmonary disease
[ ] coagulation
[ ] aid to the circulation
[ ] pain
[ ] constipation
[ ] other disease, for which _____
[ ] cortisone (tablets or injections)
[ ] sex hormones

Names of the drugs:_____
_____
_____
_____
_____
_____
_____

16.Do you now have or have you ever had <u>varicose veins</u> in the lower extremities?

(Varicose veins are clearly visible, dilated, tortuous and possibly prominent subcutaneous veins of the lower extremities).

[ ] NO
[ ] DON'T KNOW
[] YES

Where do the varicose veins exist? [ ] in left thigh / [ ] in left leg / [ ] in right thigh / [ ] in right leg
For how many years have they existed?_____ years.
When did they appear (for example after trauma/childbirth/other)?

_____

Do you now have varicose veins?	[ ] NO	[ ] YES
Are the varicose veins a cosmetic problem?	[ ] NO	[ ] YES

Have you been operated on for varicose veins?
[ ] NO
[ ] YES in left ___ times, years_____
in right ___ times, years_____

Have you received injections for varicose veins?
[ ] NO
[ ] YES in left ___ times, years_____
in right ___ times, years_____

Have you been treated for varicose veins with <u>compressive stocking</u> for more than one month?
[ ] NO
[ ] YES, for_____ months

Have you been treated for varicose veins with <u>support stocking</u>?
[ ] NO
[ ] YES, for_____ months

Have varicose veins reappeared after treatment?
[ ] NO
[ ] YES,_____ months/_____ years after the treatment.

Do you now need treatment for varicose veins?
[ ] NO [ ] YES [_] DON'T KNOW

17.Have you been operated on for any other disease?
[] NO
[] YES, which disease and when:

year _____ which operation _____

year _____ which operation _____

year _____ which operation _____

##########
Please check that you have answered all questions. A stamped and addressed envelope is included. Mail the questionnaire soon. Thank you!
##########

1989

TUTKIMUSKAAVAKE VERENKIERTOHAIRIÖISTA ALARAAJOISSA

****

SUKUNIMI _____ (ENTINEN _____)

ETUNIMET _____ **1.HENKILÖTUNNUS** __ __ __ -____
(esim.sairausvakuutuskortista)

2.SUKUPUOLI [] mies [] nainen ⌊_⌋

3.AMMATTI _____ ELÄKKEELLÄ [] ⌊_⌋⌊_⌋⌊_⌋
(nykyinen tai entinen pitkäaikainen)

OSOITE _____

4.Painonne ___ kiloa **Pituutenne** ___ senttimetriä ⌊_⌋⌊_⌋⌊_⌋

5.Onko lähisukulaisillanne (vanhemmat, isovanhemmat, sisarukset) suonikohjuja? ⌊_⌋⌊_⌋⌊_⌋
[] EI / [] EN TIEDÄ/
[] KYLLÄ,kenellä
(sukulaisuuden laatu, esim. isällä) _____ ⌊_⌋

6. Onko Teillä ollut synnytyksiä?
[] EI / [] KYLLÄ, synnytyksiä ___ kappaletta,ensimmäinen vuonna _____. ⌊_⌋⌊_⌋

7. Oletteko milloinkaan käyttänyt ehkäisypillereitä? ⌊_⌋⌊_⌋
[] EN /[] KYLLÄ, montako vuotta ___ ⌊_⌋⌊_⌋

RAVINTOAINEET JA ELINTAVAT:

8.Minkälaista maitoa käytätte?
[] Kulutusmaitoa/ []Kevytmaitoa/ [] Rasvatonta maitoa/ ⌊_⌋
[] Muuta,mitä_____
Montako lasillista (2 dl) maitoa käytätte päivässä? _____lasillista. ⌊_⌋⌊_⌋
Käytättekö ruuissanne (mm.leivässä) [] VOITA /[] MARGARIINIA/[] KASVISÖLJYÄ
[] EN KÄYTÄ NIITÄ ⌊_⌋
Montako kertaa viikon aikana syötte liha- tai makkararuokia? ____ kertaa. ⌊_⌋⌊_⌋

Montako leipäviipaletta käytätte päivässä? __ viipaletta. ⌊_⌋⌊_⌋

9.Oletteko tupakoinut säännöllisesti yli vuoden ajan elämässänne? ⌊_⌋
[] EN OLE MILLOINKAAN
[] OLEN NYT LOPETTANUT, minkä ikäisenä aloititte___ ja lopetitte___? ⌊_⌋⌊_⌋
[] TUPAKOIN; -minkä ikäisenä aloititte? _____ ikäisenä. ⌊_⌋⌊_⌋
-mitä tupakoitte [] savukkeita tai [] sikareita
[] piippua ⌊_⌋
-paljonko tupakoitte päivässä? ___ savuketta/sikaria/piipullista ⌊_⌋⌊_⌋

10.Käytättekö alkoholipitoisia juomia?

[] EN LAINKAAN TAI SATUNNAISESTI ⌊_⌋
[] KYLLÄ,paljonko seuraavista viikossa
olutta ____ pulloa(1/3 l)
viiniä ____ pulloa(3/4 l) tai ____lasillista (12 cl) ⌊_⌋⌊_⌋⌊_⌋
viinaa ____ pulloa (½ l) tai ____lasillista (4 cl)

11.Harrastatteko vapaa-aikana liikuntaa?

[] EN LAINKAAN/ [] SATUNNAISESTI/[] VIIKOITTAIN/[] USEITA KERTOJA VIIKOSSA, ⌊_⌋
mitä_____

12.Eniten tekemänne työ on/oli pääasiassa mielestänne

[] ISTUMATYÖTÄ, JOSSA TYÖPÄIVÄN AIKANA LIIKUNTAA TAI SEISOMISTA VÄHÄN (alle½t)
[] ISTUMATYÖTÄ, JOSSA TYÖPÄIVÄN AIKANA SEISOMISTA ALLE PUOLET AJASTA
[] YLI PUOLET TYÖPÄIVÄSTÄ SEISOMATYÖTÄ, ISTUMISTA AJOITTAIN TAI EI LAINKAAN
[] MUUTA KUIN EDELLÄ,minkälaista_____

JOS TEITTE SEISOMATYÖTÄ, OLIKO SEISOMATYÖSSÄ PAIKALLAANOLOA?
[]EI
[]KYLLÄ,montako tuntia päivässä keskimäärin? ___ tuntia.
MONTAKO VUOTTA TEITTE TÄTÄ TYÖTÄ? _____ vuotta.

AIKAISEMPI TERVEYDENTILANNE:

13.Onko Teillä esiintynyt pitempää lääkärinhoitoa vaatineita sairauksia?

[] EI

[] KYLLÄ (vastaa seuraaviin; rastita EI ruutu, jos kysyttyä sairautta ei ole Teillä ollut, KYLLÄ vaihtoehdoissa vastaa myös lisäkysymyksiin)

ONKO TEILLÄ OLLUT TAI ONKO NYT

- sokeritautia [] EI [] KYLLÄ,milloin alk._____
- kohonnutta verenpainetta [] EI [] KYLLÄ,milloin alk._____
- sydäninfarktia [] EI [] KYLLÄ,milloin _____
- sydämen sepelvaltimosairautta (=angina pectoris) [] EI [] KYLLÄ,milloin alk._____
- sydämen vajaatoimintaa [] EI [] KYLLÄ
- hengityselinten sairautta [] EI [] KYLLÄ,mikä _____
- alaraajan pinnallista laskimotukosta [] EI [] KYLLÄ,milloin _____ kumpi jalka []oikea/ []vasen
- alaraajan syvää laskimotukosta [] EI [] KYLLÄ,milloin _____ kumpi jalka []oikea/ []vasen
- keuhkoveritulppaa [] EI [] KYLLÄ,milloin _____
- selkäsairautta tai iskiasta [] EI [] KYLLÄ,milloin _____
- munuaissairautta [] EI [] KYLLÄ
- alaraajojen murtumia [] EI [] KYLLÄ,milloin_____ kumpi jalka []oikea/ []vasen
  missä kohdassa? _____
- alaraajojen ruhjeitten aiheuttamia pitkäaikaisia vammoja? [] EI [] KYLLÄ,milloin_____ kumpi jalka []oikea/ []vasen
- alaraajojen valtimoverenkiertohäiriöitä [] EI [] KYLLÄ,milloin alk. _____ kumpi jalka []oikea/ []vasen
- aivoverenkiertohäiriöitä [] EI [] KYLLÄ,milloin _____
- säärihaavaa [] EI [] KYLLÄ,milloin alk._____ kumpi jalka []oikea/ []vasen
- muu pitkäaikainen tai vaikea sairaus, mikä_____
  milloin_____

14.Onko Teillä esiintynyt useamman kerran tai pitkäaikaisesti alaraajoissa jokin seuraavista (jos vastaat KYLLÄ, rastita kummassa jalassa)

- jalka tuntuu raskaalta iltaa kohden [] EI [] KYLLÄ -[]OIKEA/[]VASEN
- särkyä, pistelyä päivän mittaan [] EI [] KYLLÄ -[]OIKEA/[]VASEN
- turvotusta nilkan tai säären alueella [] EI [] KYLLÄ -[]OIKEA/[]VASEN
- turvotusta reiden alueella [] EI [] KYLLÄ -[]OIKEA/[]VASEN
- aina seistessä ilmenevä säären voimakas kipu [] EI [] KYLLÄ -[]OIKEA/[]VASEN
- jalkojen palelua [] EI [] KYLLÄ -[]OIKEA/[]VASEN
- jalkojen puutumista [] EI [] KYLLÄ -[]OIKEA/[]VASEN
- suonenvetoa jaloissa [] EI [] KYLLÄ -[]OIKEA/[]VASEN
- tummanruskea ja pysyvä värimuutos nilkan tai säären ihossa [] EI [] KYLLÄ -[]OIKEA/[]VASEN
- katkokävelyoire (kävellessä pysähtymään pakottava kipu pohkeessa tai pakarassa) [] EI [] KYLLÄ -[]OIKEA/[]VASEN
- levossa ollessa kipua jalassa [] EI [] KYLLÄ -[]OIKEA/[]VASEN
- pitkäaikainen haavauma tai kuolio jalkaterän tai säären alueella [] EI [] KYLLÄ -[]OIKEA/[]VASEN
- jos jaloissa on joitakin kysytyistä oireista,
  helpottaako jalan kohottaminen oireita? [] EI [] KYLLÄ
  helpottaako jalan riiputtaminen oireita? [] EI [] KYLLÄ
- jokin muu oire, mikä_____
  _____

15.Käytättekö säännöllistä lääkitystä?

[]EN

[]KYLLÄ, mihin sairauteen tai minkä lääkeaineryhmän lääkkeitä?

[] sokeritautiin
[] verenpaineeseen
[] sepelvaltimotautiin
[] rytmihäiriöihin
[] sydämen vajaatoimintaan
[] hengityselinten sairauteen
[] veren hyytymiseen
[] verenkierron parantamiseen
[] särkyihin (mukaanlukien mm. Aspirin)
[] ummetukseen
[] muuhun sairauteen, mihin _____
[] kortisonia (tabletteina tai pistoksina)
[] nais- tai miessukuhormonia

Lääkkeiden nimet:_____
_____
_____
_____
_____
_____
_____

16.Onko Teillä nyt tai onko ollut alaraajoissa suonikohjuja?

(Suonikohjuilla tarkoitetaan selvästi näkyvää, laajentunutta, mutkittelevaa ja mahdollisesti pullottavaa alaraajan ihonalaista laskimosuonta).

[] EI(siirry kys.17.)
[] EN TIEDÄ
[] ON NYT TAI ON OLLUT)vastatkaa seuraaviin:
Millä kohdalla? []vasen reisi/ []vasen sääri/ []oikea reisi/ []oikea sääri ___
Kuinka kauan kohjut ovat olleet? _____vuotta. ___
Missä yhteydessä kohjut tulivat (esim. vamman/raskauden/muun jälkeen)?

_____

Onko Teillä tällä hetkellä suonikohjuja? [] EI [] KYLLÄ ___
Onko kohjuista Teille ulkonäöllistä haittaa? [] EI [] KYLLÄ ___

Onko Teitä leikattu suonikohjujen takia?
[] EI
[] KYLLÄ vasen jalka __ kertaa,vuosina _____ ___
oikea jalka __ kertaa,vuosina _____ ___
Onko suonikohjuja hoidettu lääkeainetta ruiskuttamalla?
[] EI
[] KYLLÄ vasen jalka __ kertaa, vuosina _____ ___
oikea jalka __ kertaa, vuosina _____ ___
Onko suonikohjuihin käytetty puristussukkahoitoa säännöllisesti yli kuukauden ajan?(ei tarkoiteta ns. tukisukkaa)
[]EI
[]KYLLÄ,___ kk ajan ___

Onko suonikohjuihin käytetty ns. tukisukkaa?
[] EI
[] KYLLÄ, ___ kk ajan. ___

Ovatko suonikohjut uusiutuneet hoitojen (leikkaukset,ruiskutukset ym.) jälkeen?
[]EIVÄT
[]KYLLÄ, kuinka pian:_____kuukautta tai ____ vuotta hoidon jälkeen ____

Tarvitsetteko mielestänne tällä hetkellä hoitoa suonikohjujen takia?
[] EN []KYLLÄ [] EN OSAA SANOA ___

17.Onko Teitä leikattu muun sairauden takia?
[] EI
[] KYLLÄ, minkä ja milloin:

v._____ leikkaus_____

v._____ leikkaus_____

v._____ leikkaus_____
(jatka tarvittaessa)

##########

OLKAA HYVÄ JA TARKISTAKAA, ETTÄ VASTASITTE KAIKKIIN KOHTIIN OHJEIDEN MUKAISESTI. SULKEKAA KYSYMYSLOMAKE (4 SIVUA) MUKANA SEURANNEESEEN OSOITTEELLA VARUSTETTUUN KIRJEKUOREEN (POSTIMAKSU ON MAKSETTU) JA JÄTTÄKÄÄ SE POSTIIN PIAN. KIITOS!

##########

QUESTIONNAIRE ON CIRCULATORY PROBLEMS IN THE LOWER EXTREMITIES (1994)

SURNAME_____ FORENAME_____ GENDER [_] male [_] female

DATE OF BIRTH OR SOCIAL SECURITY NUMBER __ __ __ - ____

Address _____
Profession _____

[_] senior clerical worker
[_] clerical worker
[_] worker
[_] other _____

Education:
[_] University
[_] College
[_] Vocational school
[_] High school
[_] Comprehensive school
[_] Other _____

Weight _____ kg and Height _____ cm

DIET AND HABITS:

What kind of milk do you drink?
[_] WHOLE MILK
[_] SEMI-SKIMMED MILK
[_] SKIMMED MILK
[_] OTHER, WHAT KIND? _____
How many glasses (2dl) of milk daily? _____ GLASSES
Do you use (e.g. in food and on bread)
[_] BUTTER
[_] MARGARINE
[_] VEGETABLE OIL
[_] NONE OF THESE

For how many times each week do you eat meals of meat or sausages? _____ times
How many slices of bread do you eat each day? _____ slices

Have you ever smoked for longer than one year?
[_] NEVER
[_] I HAVE STOPPED SMOKING, at what age did you start ____ and stop ____?
[_] I NOW SMOKE, at what age did you start? _____
Do you smoke
[_] CIGARETTES, [_] CIGARS OR [_] PIPE ?
How much each day? ____ cigarettes/cigars/pipefuls

Do you use alcohol?
[_] NOT AT ALL OR OCCASIONALLY
[_] YES, how much per week
beer in bottles (1/3 l) ____
wine in bottles (3/4 l) ____ or in glasses (12 cl) ____
spirits in bottles (1/2 l) ____ or in glasses (4 cl) ____

Women: Have you ever given birth?
[_] NO [_] YES, HOW MANY TIMES? ____ , YEAR OF THE FIRST BIRTH ____.

Women: Have you ever used contraceptive pills?
[_] NO
[_] YES, how many years? ____.
At what ages did you start using contraceptive pills? __ At what ages did you stop using contraceptive pills? __

Women: Have you ever used hormone replacement therapy?
[_] NO
[_] YES, how many years? ____.
At what ages did you start using contraceptive pills? __ At what ages did you stop using contraceptive pills? __

Which of the following applies to the posture normally assumed in your main (past or present) occupation?
[_] SITTING WITH LESS THAN ½ HOUR OF STANDING IN A DAY.
[_] MAINLY SITTING, WITH LESS THAN HALF THE WORKING DAY SPENT STANDING.
[_] STANDING FOR OVER HALF OF THE WORKING DAY.
[_] OTHER, what posture _____

How many years? ____ years
If you worked on your feet, did you work in a static standing posture?
[_] NO [_] YES, for how many hours daily (on average)? _____ hours

PREVIOUS HEALTH:

Have you ever suffered following conditions requiring medical care?
[_] NO
[_] YES, which of these?

-diabetes	[_] NO [_] YES, since _____
-high blood pressure	[_] NO [_] YES, since _____
-cardiac infarct	[_] NO [_] YES, since _____
-angina pectoris	[_] NO [_] YES, since _____
-insufficiency of the heart	[_] NO [_] YES, since _____
-pulmonary diseases	[_] NO [_] YES, which disease _____
-superficial thrombosis in lower extremities	[_] NO [_] YES, since _____ in which leg? [_] right/[_]left
-deep venous thrombosis in lower extremities	[_] NO [_] YES, since _____ in which leg? [_] right/[_]left
-pulmonary embolism	[_] NO [_] YES, since _____
-sciatica or other back problems	[_] NO [_] YES, since _____
-renal diseases	[_] NO [_] YES, since _____
-problems in arterial circulation of the legs	[_] NO [_] YES, since _____ in which leg? [_] right/[_]left
-cerebral circulatory problems	[_] NO [_] YES, since _____
-ulceration in leg	[_] NO [_] YES, since _____ in which leg? [_] right/[_]left

-other chronic or severe disease, which disease? _____, since _____

Have you had a frequent or prolonged experience of the following conditions during last month? (In which leg?)

-sensation of heavy leg(s) in the afternoon	[_] NO [_] YES -> [_]RIGHT/[_]LEFT
-pain or prickly sensation in leg(s) during the daytime	[_] NO [_] YES -> [_]RIGHT/[_]LEFT
-swelling of ankle or leg(s)	[_] NO [_] YES -> [_]RIGHT/[_]LEFT
-swelling of thigh(s)	[_] NO [_] YES -> [_]RIGHT/[_]LEFT
-considerable leg-pain while standing	[_] NO [_] YES -> [_]RIGHT/[_]LEFT
-cold legs	[_] NO [_] YES -> [_]RIGHT/[_]LEFT
-numbness in leg(s)	[_] NO [_] YES -> [_]RIGHT/[_]LEFT
-cramps in leg(s)	[_] NO [_] YES -> [_]RIGHT/[_]LEFT
-permanent change in the color of the skin in ankle or leg	[_] NO [_] YES -> [_]RIGHT/[_]LEFT
-intermittent claudication (explained)	[_] NO [_] YES -> [_]RIGHT/[_]LEFT
-lower-extremity pain while at rest	[_] NO [_] YES -> [_]RIGHT/[_]LEFT
-longstanding ulceration or necrosis in foot or leg	[_] NO [_] YES -> [_]RIGHT/[_]LEFT

[_] NONE OF THE ABOVEMENTIONED SYMPTOMS

Are you on permanent medication?
[_] NO
[_] YES, for/medication is

[_] diabetes
[_] hypertension
[_] coronary disease
[_] arrhythmia
[_] insufficiency of the heart
[_] pulmonary disease
[_] coagulation
[_] aid to the circulation
[_] pain
[_] constipation
[_] other disease, for which _____
[_] cortisone (tablets or injections)
[_] sex hormones

List the names of the drugs: _____
_____
_____
_____
_____
_____
_____
_____

Do you now have or have you ever had varicose veins in the lower extremities?

(Varicose veins are clearly visible, dilated, tortuous and possibly prominent subcutaneous veins of the lower extremities).
[_] NO
[_] DON'T KNOW
[_] YES
[_] YES, BUT NOT ANYMORE, BECAUSE THEY [_] HAVE BEEN OPERATED ON /[_] HAVE DISAPPEARED

Where do the varicose veins exist?
[_] in left thigh
[_] in left leg
[_] in right thigh
[_] in right leg

How old were you when varicose veins appeared? _____ years old

Are the varicose veins a cosmetic problem?
[_] NO [_] YES

Have you been operated on for varicose veins?
[_] NO [_] YES, how many times? _____, when? (years) _____

Where have you been operated on for varicose veins?
[_] in a regional hospital
[_] in Hatanpää City Hospital
[_] in Tampere University Hospital
[_] in another central hospital, which _____
[_] in a private hospital
[_] in another hospital, which_____

Have you received injections for varicose veins?
[_] NO [_] YES

Where have you received injections for varicose veins?

[_] in a regional hospital
[_] in Hatanpää City Hospital

[_] in Tampere University Hospital
[_] in another central hospital, which _____
[_] in a private hospital
[_] in another hospital, which_____

Have varicose veins reappeared after treatment?
[_] NO [_] YES

Do you now need treatment for varicose veins?
[_] NO [_] DON'T KNOW [_] YES,
What kind of treatment?
[_] counseling
[_] examination or treatment
[_] other, what? _____

Are you waiting for treatment for varicose veins?
[_] NO
[_] YES, [_] operation [_] other treatment

Have you been treated for varicose veins with compressive stocking for more than one month?
[_] NO [_] YES

Have you been treated for varicose veins with support stocking?
[_] NO [_] YES

Do you closest relatives (parents, grandparents or siblings) have varicose veins?
[_] NO [_] DON'T KNOW [_] YES, who _____

Have you been operated on for any other disease?
[_] NO
[_] YES, which disease and when:

year _____ which operation _____

year _____ which operation _____

year _____ which operation _____

##########
Please check that you have answered all questions. A stamped and addressed envelope is included. Mail the questionnaire soon. Thank you!
##########

1994

TUTKIMUSLOMAKE VERENKIERTOHÄIRIÖISTÄ ALARAAJOISSA

****

SUKUNIMI _____ **ETUNIMET** _____ **SUKUPUOLI** [_] mies [_] nainen

SYNTYMÄAIKA/SOTU (esim.sairausvakuutuskortista) __ __ __ -___

Osoitteenne _____

Ammattinne _____

Oletteko viimeisimmän ammattinne mukaisesti :
[_] YLEMPI TOIMIHENKILÖ
[_] ALEMPI TOIMIHENKILÖ
[_] TYÖNTEKIJÄ
[_] MUU, MIKÄ?_____

Koulutuksenne on
[_] YLIOPISTO TAI KORKEAKOULU
[_] OPISTOTASOINEN KOULUTUS
[_] AMMATTIKOULU TAI VASTAAVA
[_] LUKIO TAI OPPIKOULU
[_] KANSAKOULU,
[_] MUU, MIKÄ _____

Nykypainonne ___ kiloa ja **Pituutenne** ___ senttimetriä

RAVINTOAINEET JA ELINTAVAT:

Minkälaista maitoa käytätte?
[_] KULUTUSMAITOA
[_] KEVYTMAITOA
[_] RASVATONTA MAITOA/
[_] MUUTA,MITÄ_____
Montako lasillista (2 dl) maitoa käytätte päivässä? ____LASILLISTA.
Käytättekö ruuissanne (mm.leivässä)
[_] VOITA
[_] MARGARIINIA
[_] KASVISÖLJYÄ
[_] EN KÄYTÄ NIITÄ

Montako kertaa viikon aikana syötte liha- tai makkararuokia? ____ kertaa.
Montako leipäviipaletta käytätte päivässä? __ viipaletta.

Oletteko tupakoinut säännöllisesti yli vuoden ajan elämässänne?
[_] EN OLE MILLOINKAAN
[_] OLEN NYT LOPETTANUT, minkä ikäisenä aloititte___ ja lopetitte___?
[_] TUPAKOIN EDELLEEN; minkä ikäisenä aloititte? _____ Ikäisenä.
Mitä tupakoitte?
[_] SAVUKKEITA , [_] SIKAREITA VAI [_] PIIPPUA
Paljonko tupakoitte päivässä? ___ **savuketta/sikaria/piipullista**

Käytättekö alkoholipitoisia juomia?
[_] EN LAINKAAN TAI SATUNNAISESTI
[_] KYLLÄ,paljonko seuraavista viikossa
olutta ____ pulloa(1/3 l)
viiniä ____ pulloa(3/4 l) tai ____lasillista (12 cl)
viinaa ____ pulloa (½ l) tai ____lasillista (4 cl)

Naiset: Onko **Teillä ollut synnytyksiä?**
[_] EI [_] KYLLÄ, SYNNYTYKSIÄ ___ KAPPALETTA, ENSIMMÄINEN VUONNA _____.

Naiset: Oletteko milloinkaan käyttänyt ehkäisypillereitä ?
[_] EN
[_] KYLLÄ, montako vuotta ___.
Minkä ikäisenä aloititte pillerit? ____Vuotiaana. Minkä ikäisenä lopetitte ne? ____Vuotiaana.

Naiset: Oletteko milloinkaan käyttänyt naissukuhormonia ?
[_] EN
[_] KYLLÄ, montako vuotta ___.
Minkä ikäisenä aloititte ? ____Vuotiaana. Minkä ikäisenä lopetitte ? ____Vuotiaana.

Eniten tekemänne työ on/oli pääasiassa mielestänne
[_] ISTUMATYÖTÄ, JOSSA TYÖPÄIVÄN AIKANA LIIKUNTAA TAI SEISOMISTA VÄHÄN (alle ½ t)
[_] ISTUMATYÖTÄ, JOSSA TYÖPÄIVÄN AIKANA SEISOMISTA ALLE PUOLET AJASTA
[_] YLI PUOLET TYÖPÄIVÄSTÄ SEISOMATYÖTÄ, ISTUMISTA AJOITTAIN TAI EI LAINKAAN
[_] MUUTA KUIN EDELLÄ,minkälaista_____

Montako vuotta teitte tätä ilmoittamaanne työtä? _____ vuotta.
Jos teitte seisomatyötä, oliko seisomatyössänne paikallaanoloa?
[_]EI [_]KYLLÄ, montako tuntia päivässä keskimäärin? ___ tuntia.

AIKAISEMPI TERVEYDENTILANNE:

Onko Teillä esiintynyt allalueteltuja, pitempää lääkärinhoitoa vaatineita sairauksia?
[_] EI
[_] KYLLÄ (vastatkaa seuraaviin; rastittakaa EI ruutu, jos kysyttyä sairautta ei ole Teillä ollut, KYLLÄ vaihtoehdoissa vastatkaa myös lisäkysymyksiin)

ONKO TEILLÄ OLLUT TAI ONKO NYT

- sokeritautia [_] EI [_] KYLLÄ,milloin alk._____
- kohonnutta verenpainetta [_] EI [_] KYLLÄ,milloin alk._____
- sydäninfarktia [_] EI [_] KYLLÄ,milloin _____
- sydämen sepelvaltimosairautta (=angina pectoris) [_] EI [_] KYLLÄ,milloin alk._____
- sydämen vajaatoimintaa [_] EI [_] KYLLÄ, -"- _____
- hengityselinten sairautta [_] EI [_] KYLLÄ,mikä _____
- alaraajan pinnallista laskimotukosta [_] EI [_] KYLLÄ,milloin _____ kumpi jalka [_]oikea/ [_]vasen
- alaraajan syvää laskimotukosta [_] EI [_] KYLLÄ,milloin _____ kumpi jalka [_]oikea/ [_]vasen
- keuhkoveritulppaa [_] EI [_] KYLLÄ,milloin _____
- selkäsairautta tai iskiasta [_] EI [_] KYLLÄ,milloin _____
- munuaissairautta [_] EI [_] KYLLÄ -"- _____
- alaraajojen valtimoverenkiertohäiriöitä [_] EI [_] KYLLÄ,milloin alk. _____ kumpi jalka [_]oikea/ [_]vasen
- aivohalvausta tai muuta aivoverenkiertohäiriöitä [_] EI [_] KYLLÄ,milloin _____
- säärihaavaa [_] EI [_] KYLLÄ,milloin alk._____ kumpi jalka [_]oikea/ [_]vasen
- muuta pitkäaikaista tai vaikeaa sairautta, mikä_____ milloin todettu? Vuonna _____

Onko Teillä esiintynyt useamman kerran tai pitkäaikaisesti alaraajoissa viimeksi kuluneen kuukauden aikana jokin seuraavista
(jos vastaatte KYLLÄ, rastittakaa kummassa jalassa)

- jalka tuntuu raskaalta iltaa kohden [_] EI [_] KYLLÄ ->[_]OIKEA/[_]VASEN
- särkyä, pistelyä päivän mittaan [_] EI [_] KYLLÄ ->[_]OIKEA/[_]VASEN
- turvotusta nilkan tai säären alueella [_] EI [_] KYLLÄ ->[_]OIKEA/[_]VASEN
- turvotusta reiden alueella [_] EI [_] KYLLÄ ->[_]OIKEA/[_]VASEN
- aina seistessä ilmenevä säären voimakas kipu [_] EI [_] KYLLÄ ->[_]OIKEA/[_]VASEN
- jalkojen palelua [_] EI [_] KYLLÄ ->[_]OIKEA/[_]VASEN
- jalkojen puutumista [_] EI [_] KYLLÄ ->[_]OIKEA/[_]VASEN
- suonenvetoa jaloissa [_] EI [_] KYLLÄ ->[_]OIKEA/[_]VASEN
- tummanruskea ja pysyvä värimuutos nilkan tai säären ihossa [_] EI [_] KYLLÄ ->[_]OIKEA/[_]VASEN
- katkokävelyoire (kävellessä pysähtymään pakottava kipu pohkeessa tai pakarassa) [_] EI [_] KYLLÄ ->[_]OIKEA/[_]VASEN
- levossa ollessa kipua jalassa [_] EI [_] KYLLÄ ->[_]OIKEA/[_]VASEN
- pitkäaikainen haavauma tai kuolio jalkaterän tai säären alueella [_] EI [_] KYLLÄ ->[_]OIKEA/[_]VASEN

[_] EI MITÄÄN EDELLÄLUETELLUISTA OIREISTA

Käytättekö nyt säännöllistä lääkitystä?
[_]EN
[_]KYLLÄ, mihin sairauteen tai minkä lääkeaineryhmän lääkkeitä?

[_] sokeritautiin
[_] verenpaineeseen
[_] sepelvaltimotautiin
[_] rytmihäiriöihin
[_] sydämen vajaatoimintaan
[_] hengityselinten sairauteen
[_] veren hyytymiseen
[_] verenkierron parantamiseen
[_] särkyihin (mukaanlukien mm. Aspirin)
[_] ummetukseen
[_] muuhun sairauteen, mihin _____
[_] kortisonia (tabletteina tai pistoksina)
[_] nais- tai miessukuhormonia

Lääkkeidenne nimet: _____
_____
_____
_____
_____
_____
_____
_____

Onko Teillä nyt tai onko joskus ollut alaraajoissa suonikohjuja?

(Suonikohjuilla tarkoitetaan selvästi näkyvää, laajentunutta, mutkittelevaa ja mahdollisesti pullottavaa alaraajan ihonalaista laskimosuonta).
[_] EI
[_] EN TIEDÄ
[_] ON NYT
[_] ON OLLUT, MUTTA NYT EI KOSKA NE OVAT [_] HOIDETUT /[_] HÄVINNEET ITSESTÄÄN

Missä suonikohjuja on (rastittakaa kaikki esiintymispaikat)?
[_]vasen reisi
[_]vasen sääri
[_]oikea reisi
[_]oikea sääri

Missä iässä suonikohjut tulivat? _____vuotiaana.

Onko kohjuista Teille ulkonäöllistä haittaa?
[_] EI [_] KYLLÄ

Onko Teitä milloinkaan leikattu suonikohjujen takia?
[_] EI [_] KYLLÄ, montako kertaa? _____, minä vuosina?_____

Missä leikkaus tai leikkaukset tehtiin (valitkaa kaikki Teihin sopivat vaihtoehdot)?
[_] aluesairaalassa
[_] Hatanpään sairaalassa
[_] Tampereen keskussairaalassa/TAYSissa
[_] muussa keskussairaalassa, missä_____
[_] yksityissairaalassa Suomessa
[_] muussa paikassa(esim ulkomailla), missä? _____

Onko suonikohjuja hoidettu ruiskuttamalla lääkettä niihin?
[_] EI [_] KYLLÄ, vuosina _____

Missä ruiskutus tehtiin (valitkaa kaikki Teihin sopivat vaihtoehdot)?
[_] aluesairaalassa
[_] Hatanpään sairaalassa
[_] Tampereen keskussairaalassa/TAYSissa
[_] muussa keskussairaalassa, missä_____
[_] yksityissairaalassa Suomessa
[_] muussa, (esim ulkomailla), missä? _____

Ovatko suonikohjut uusiutuneet hoitojen (leikkaukset,ruiskutukset ym.) jälkeen?
[_]EIVÄT [_]KYLLÄ

Tarvitsetteko mielestänne tällä hetkellä hoitoa suonikohjujen takia?
[_] EN [_] EN OSAA SANOA [_]KYLLÄ
Jos vastasitte kyllä, minkälaista hoitoa?
[_] neuvontaa esim terveydenhoitajalta
[_] lääkärintutkimusta tai -hoitoa
[_] muuta, mitä _____

Oletteko tällä hetkellä odottamassa lääkärin määräämää hoitoa suonikohjujen takia?
[_] EN
[_] KYLLÄ, OLEN [_] suonikohjuleikkausjonossa [_] muuta suonikohjujen hoitoa odottamassa

Oletteko suonikohjujen takia käyttänyt mittojen mukaan valittua puristussukkaa yli kuukauden ajan?
[_]EN [_]KYLLÄ

Oletteko käyttänyt kevyempiä ns. tukisukkia?
[_] EN [_] KYLLÄ

Onko lähisukulaisillanne (vanhemmat, isovanhemmat, sisarukset) suonikohjuja?
[_] EI [_] EN TIEDÄ [_] KYLLÄ,kenellä (sukulaisuuden laatu, esim. isällä)_____

Onko Teitä leikattu muun sairauden takia?
[_] EI
[_] KYLLÄ, minkä ja milloin:

v._____ leikkaus_____

v._____ leikkaus_____

v._____ leikkaus_____ (jatkakaa tarvittaessa)

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OLKAA HYVÄ JA TARKISTAKAA, ETTÄ VASTASITTE KAIKKIIN KOHTIIN OHJEIDEN MUKAISESTI. SULKEKAA KYSYMYSLOMAKE (4 SIVUA) MUKANA SEURANNEESEEN OSOITTEELLA VARUSTETTUUN KIRJEKUOREEN JA JÄTTÄKÄÄ SE POSTIIN PIAN. KIITOS!

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ORIGINAL COMMUNICATIONS