

**PREVALENCE OF VARICOSE VEINS
AND CHRONIC VENOUS INSUFFICIENCY
OF THE LEGS
IN THE GENERAL POPULATION**

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DECLARATION OF THE CANDIDATE AND ACKNOWLEDGEMENTS

I declare that this thesis has been composed by myself.

I declare that I made a substantial contribution to the work of the Edinburgh Vein Study. I performed the literature review, consulted on methods of assessment for varicose veins and contributed to writing applications for funding and ethical approval for the Edinburgh Vein Study. I helped to train the staff in the measurement techniques, designed the study documentation, liaised with the collaborating General Practitioners and supervised the research team. I performed a proportion of the data collection, instituted quality control measures, supervised a follow-up study of non-responders and contributed to data analysis and writing up of results.

I would like to thank the following, whose roles were as follows:

- Professor Gerry Fowkes (Professor of Epidemiology, University of Edinburgh, principal grantholder and study supervisor) supervised and supported me during the study.
- Professor Vaughan Ruckley (Professor of Vascular Surgery, Royal Infirmary of Edinburgh, and co-grantholder) gave clinical advice during the study.
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- Dr. Amanda Lee (Statistician, University of Edinburgh) gave statistical advice on the study, and performed most of the analysis.

- Ms. Maggie Carson (research nurse) and Mrs. Eileen Kerracher (technician) performed the majority of data collection.
- Ms. Laura Diamond (medical student) worked on the survey of non-responders.
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- Mr. Grant Didcock and Mr. Toby Blake provided statistical support.
- Dr. M-T. Widmer and the late Professor L.K. Widmer provided background information and taught me the Basle Study classification.
- Mr. Bill Manson (my husband) provided advice and support throughout the study and the writing of this thesis.

Several of the above are co-authors on research papers arising from the work of the Edinburgh Vein Study. A book chapter containing part of the literature review from this thesis has also been published (details appended).

I declare that work on the prevalence of trunk varicose veins from the Edinburgh Vein Study, including an abbreviated literature review, formed the basis for one of my reports for Part II of the Membership of the Faculty of Public Health Medicine examination. This report has been submitted for the September 2000 sitting of the examination.

Christine Evans

14th July 2000

ABSTRACT

Venous disease of the legs is a common condition which causes considerable morbidity to affected patients and significant cost to the Health Service. Exactly how common varicose veins and chronic venous insufficiency (CVI) are in the community is difficult to determine because relatively few population-based epidemiological studies have been carried out. Many previous studies have investigated samples of clinic patients or specific occupational groups which may not be representative of the general population.

The overall aim of the Edinburgh Vein Study was to determine the prevalence of venous disease in the general population, and to identify associated genetic and lifestyle risk factors, with a long term view of establishing measures for prevention. The specific objectives of this thesis were to determine the prevalence of varicose veins and CVI on clinical examination, and venous reflux on duplex scanning, in a random sample of the general population. The study design was a cross-sectional survey and the initial study population will be followed up as a cohort. The target population was men and women aged 18-64 years living in the city of Edinburgh. Subjects were randomly selected from the age-sex registers of 12 general practices which were distributed geographically and socio-economically throughout the city. Information collected on each subject included demographic data and past medical history from a questionnaire; height and weight measurement; classification of varicose veins and chronic venous insufficiency on clinical examination and

measurement of duration of venous reflux on duplex scanning of eight vein segments in each leg.

A total of 1566 subjects attended the study, 867 women and 699 men. The final response rate was 53.8%. The study participants were generally older, from more affluent areas and more often female than the non-responders ($p \leq 0.001$). The age-adjusted prevalence of trunk varices in study attenders was 40% in men and 32% in women ($p \leq 0.01$); this sex difference was mostly due to a higher prevalence of mild trunk varices in men. More than 80% of subjects had hyphenweb and reticular varices. The age-adjusted prevalence of CVI was 9% in men and 7% in women ($p \leq 0.05$). The prevalence of all categories of venous disease increased with age. There was no significant association between trunk varices or CVI and social class, and no consistent relationship with body mass index. Women were more likely to have had treatment for varicose veins than men.

On duplex scanning, the prevalence of venous reflux was similar in the right and left legs. The highest prevalence of reflux ≥ 0.5 seconds was in the lower thigh long saphenous vein (LSV) segment (right leg 18.6%, left leg 17.5%). Men had a higher prevalence of reflux in the deep vein segments compared to women, while women had a (non-significantly) higher prevalence in the superficial vein segments. The prevalence of reflux tended to increase with age in many vein segments (lower thigh LSV, test for linear association $p \leq 0.001$). Although prevalence of reflux was related to the presence and severity of venous disease, it was also present in many without clinically apparent disease. There was considerable overlap in reflux duration

between subjects with and without venous disease and the cut-off point at which reflux duration became significant was not clear-cut.

The Edinburgh Vein Study confirms that venous disease is a common condition which increases with age. Contrary to many previous studies, the results suggest that varicose veins and CVI are at least as common in men as women. A positive association was seen between the prevalence of venous reflux in individual vein segments and the presence and severity of venous disease, although reflux was also present in many with no clinical signs of disease.

Follow-up of this cohort will provide information on the incidence, natural history and development of venous disease in both sexes. It will also help to clarify the extent to which venous reflux is a predictor of future occurrence of venous disease and of complications in those who already have disease. Further long term studies are required to determine the extent to which treatment prevents progression of venous disease. Such information on the natural history and outcomes of treatment is required to allow clinicians and policy makers to make rational decisions as to who will benefit most from medical intervention for venous disease.

ABBREVIATIONS

AVP	Ambulatory venous pressure
BMI	Body mass index
CEAP	Classification system for chronic venous disease based on clinical signs (C), cause (E (etiology)), anatomic distribution (A) and pathophysiologic condition (P)
CFV	Common femoral vein
cm	centimetre
CVI	Chronic venous insufficiency
Depcat	Deprivation category
Depscore	Deprivation score
EVS	Edinburgh Vein Study
GP	General Practitioner
GRO	General Register Office
ISD, NHSiS	Information and Statistics Division National Health Service in Scotland
kg	kilogram
LSV	Long saphenous vein
NHS	National Health Service
OPCS	Office of Population Censuses and Surveys
RD	Reflux duration
ROC	Receiver operator curve
SFV	Superficial femoral vein

SSV

Short saphenous vein

UK

United Kingdom

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CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

Venous disease is a major problem in Western societies, resulting in considerable morbidity in the population and cost to health services (Laing 1992). Varicose veins are one of the commonest problems seen in district general hospitals (Scott et al. 1990). Although there have been recent reports of health authorities restricting the funding of varicose vein operations (Corbett 1999, Wright 1999), the evidence on which to base such decisions is lacking (Robbins et al. 1994). Information on the natural history of varicose veins and their progression to more severe venous disease is required, in order to identify which patients will benefit most from treatment. The Edinburgh Vein Study was designed to provide information on the prevalence and progression of venous disease in the population of Edinburgh.

This chapter will give an overview of venous disease, beginning with a brief history and summary of the extent of the problem. The anatomy of the venous system of the legs will be reviewed, and the spectrum and pathogenesis of venous disease will be considered. Methods of assessment of venous disease will be discussed briefly, followed by a more detailed section on duplex ultrasound, which was the method used in the Edinburgh Vein Study. Finally the aims and objectives of the Edinburgh Vein Study and of this thesis will be outlined. (Investigation into deep venous

thrombosis was not an objective of this study and this condition will not be considered in this thesis.)

1.2 BACKGROUND TO VENOUS DISEASE

1.2.1 History

The first description of varicose veins is thought to be contained in the Ebers papyrus written in 1500 B.C. Three types of lump were described and it was advised that 'certain serpentine windings are not to be operated upon'. An early depiction of a varicose vein can be seen on a tablet estimated to date from the end of the fourth century B.C. This tablet was found at the foot of the Acropolis in Athens and shows a huge lower leg with a varicose vein coursing up the medial aspect (Browse et al. 1988). Much was written about venous conditions in the Roman times. Plasters and linen roller bandages for leg ulcers were advised by Aurelius Cornelius Celsus (25 B.C. – A.D. 50). The Byzantine physician Aetius of Amida on the Tigris (A.D. 502-575) appears to have been the first to ligate varicose veins (Dodd and Cockett 1976).

The theory of humors of Claudius Galen (A.D. 130 - 200) and his idea of the to-and-fro movement of blood and its spirits, dominated medical thinking for fifteen centuries (Dodd and Cockett 1976). Varicose elongation, tortuosity and dilation were thought to be caused by the weight of stagnant blood on the walls of veins (Bergan 1991). The venous system was described in detail by Vesalius in 1555 although the first recorded drawing of a venous valve was not published until 1585 (Browse et al. 1988). In 1676 Wiseman used the term 'varicous ulcer' and first considered that

ulcers resulted directly from a circulatory defect. However it was not until the nineteenth century that the term varicose ulcer became established with the emphasis on varicose veins as the cause of leg ulcers (Dodd and Cockett 1976).

The first description of a clinical test for venous incompetence was in 1846 when Sir Benjamin Brodie described the prevention of reflux down the long saphenous vein by digital pressure (Browse et al. 1988). The origins of long saphenous vein stripping date back to the work of Madelung in 1844, while combinations of ligation surgery and sclerotherapy were first suggested in the early 20th century (Bergan 1991). The first attempts at phlebography were made in 1923 using strontium bromide, although it was not until 1954 that a suitable contrast material was introduced, making phlebography widely available (Browse et al. 1988). In recent years, the development of ultrasound imaging has contributed significantly to the anatomical and functional understanding of venous disorders (Allan 1999).

1.2.2 The extent of the problem

Venous disease is a common problem in the Western world. Exactly how common is difficult to determine, because relatively little epidemiological research has been conducted in this area. This is perhaps because venous conditions are rarely a cause of death and generally have a low public profile, despite causing considerable morbidity. It has been estimated that the prevalence of varicose veins in the Western adult population is approximately 10-15% in men and 20-25% in women (Callam 1994) and that chronic leg ulceration affects 1% of the population at some point in

their lives (Callam 1992). Surveys have shown that 57-80% of leg ulcer patients have demonstrable venous disease (Alexander House Group, 1992).

1.2.3 Socio-economic implications

At least 7,000 varicose vein operations were performed in Scotland during 1997 (Information and Statistics Division (ISD) National Health Service in Scotland (NHSiS), unpublished data). Venous disease consumes approximately 2% of the United Kingdom's (UK) healthcare resources (Laing 1992) and, at 1990-91 prices, the estimated direct annual cost to the NHS in the UK of treating leg ulcers was £230-400 million (Bosanquet 1992). Leg ulcers are not just limited to the elderly; one study found that most leg ulcer patients had experienced ulceration during their working life and concluded that the condition affects the earning capacity of 40% of those affected who are working (Callam et al. 1988). In addition to monetary costs, quality of life assessments have shown that physical complaints increase with more severe chronic venous insufficiency (CVI) (Augustin et al. 1997). Patients with venous ulceration suffer pain, depression and anxiety (Franks et al. 1994) with the condition having a major impact on social life, mobility and sleep quality (Franks 1999).

1.3 VENOUS SYSTEM OF THE LOWER LIMB

In order to understand the pathogenesis of venous disease, the normal anatomy and functioning of the lower limb venous system needs to be considered.

1.3.1 Venous return

In the lower limb, large superficial veins lie in the subcutaneous tissues; deep veins which accompany the arteries lie within the musculature (McMinn 1990) (Figure 1.1). The superficial and deep veins are connected by communicating vessels or perforating veins, found particularly in the ankle region and the medial side of the lower leg (Snell 1981). Muscles, mainly located in the calf and the foot, compress the deep veins when they contract. This action pumps blood from the periphery up towards the heart. When the deep veins are emptied, blood is sucked in from the superficial veins via the perforators. Reflux or reverse flow of blood is prevented by one-way valves in the veins (Hobbs 1991).

1.3.2 Superficial veins

The superficial veins of the leg are the great (long) and small (short) saphenous veins and their tributaries (Figure 1.1). The medial end of the dorsal venous arch of the foot drains into the long saphenous vein (LSV) which runs upwards in front of the medial malleolus. The LSV ascends in the superficial fascia along the length of the antero-medial aspect of the leg, passes behind the knee and forward around the medial side of the thigh. It passes through the saphenous opening in the deep fascia 3cm below

and lateral to the public tubercle, to join the antero-medial side of the (common) femoral vein (CFV). The short saphenous vein (SSV) begins as a continuation of the lateral part of the dorsal venous arch of the foot. It ascends behind the lateral malleolus, follows the lateral border of the achilles tendon and then runs up the middle of the back of the lower leg. The vein pierces the deep fascial roof of the popliteal fossa and passes between the two heads of the gastrocnemius muscle. The termination of the SSV varies: in around 60% of cases the vein joins the popliteal vein in the popliteal fossa within 8 cm of the knee joint; in 20% of cases, it joins the LSV at varying levels in the thigh; in the remainder of cases, it has an alternative termination eg. by joining the superficial or deep femoral vein (Browse et al. 1988, McMinn 1990, Snell 1981).

1.3.3 Deep veins

The principal conducting deep veins below the knee are usually double channels which correspond to the three main arteries, the anterior and posterior tibial and the peroneal. At the lower border of the popliteus muscle, the anterior and posterior tibial veins join to form the popliteal vein. This then ascends through the popliteal fossa, passes through the opening in the adductor magnus muscle to become the (superficial) femoral vein (SFV). The SFV ascends through the thigh, and receives the profunda femoris vein approximately 9cm below the inguinal ligament forming the CFV. The LSV joins its anteromedial side just below the femoral sheath. The CFV leaves the thigh within the femoral sheath, and passes behind the inguinal

ligament to become the external iliac vein (Browse et al. 1988, McMinn 1990, Snell 1981, Tibbs 1992).

1.3.4 Venous valves

The veins of the lower limb contain thin, bicuspid valves which are arranged so that blood can only flow in the direction of the heart. Perforating veins possess valves that prevent the flow of blood from the deep to the superficial veins (Snell 1981). The valves are formed from a thin layer of collagen fibres covered with endothelium. There is much variation in the number and quality of valves present in veins. The inferior vena cava and common iliac veins have no valves. In addition, 75% of the external iliac and 25% of the common femoral vein are valveless. The number of valves in each vein segment below the inguinal ligament steadily increases and by the level of the calf veins valves are spaced 5cm apart. However, veins and venules smaller than 1 mm in diameter do not possess valves (Browse et al. 1988). Patients may lack the usual number of valves due to an inborn deficiency or valves may be absent in congenital venous abnormalities. Deep vein thrombosis may damage valves making them ineffective. Figure 1.2 shows the upward flow of blood through a venous valve, and the reverse flow or venous reflux resulting from valvular incompetence (Tibbs 1992). Such reflux can be detected using Doppler ultrasound.

1.4 VENOUS DISEASE

1.4.1 Spectrum of disease

Chronic venous disease is defined as 'an abnormally functioning venous system caused by venous valvular incompetence with or without associated venous outflow obstruction, which may affect the superficial venous system, the deep venous system, or both' (Porter et al 1995). The spectrum of disease ranges from minor asymptomatic incompetence of the venous valves through hyphenweb (intradermal), reticular (subdermal) and subcutaneous varicose veins, to CVI and venous ulceration. CVI ranges in severity of presentation from a submalleolar venous 'flare' at the ankle to areas of hypo- and hyper-pigmentation in the gaiter area with oedema and subcutaneous fibrosis, progressing to eczematoid changes and eventual ulceration (Porter et al. 1988, 1995, Widmer 1978).

1.4.2 Pathogenesis

'Primary' varicose veins are those which arise without an obvious cause rather than being 'secondary' to another pathological process (Burnand 1999). Several theories for the pathogenesis of primary varicose veins have been suggested. In the valvular hypothesis, the primary defect is postulated to be in the vein valves which fail sequentially from above the saphenofemoral junction downwards. Exposure to transient high pressure leads to incompetence of the saphenofemoral valves. Repetition of the process eventually results in dilatation and varicosity of the thin walled branches of the saphenous vein (Ludbrook 1986). However, evidence to support this theory is lacking (Browse et al. 1988).

The vein wall hypothesis suggests that the primary defect is a 'weakness' of the wall of the vein which dilates under pressure (Rose 1986). Changes in the collagen, elastin and smooth muscle content of affected veins have been proposed, and significantly reduced vein wall elasticity has been detected in affected patients (Burnand 1999). Other theories of causation of subcutaneous varices include exposure to high pressure due either to the presence of multiple small arterio-venous anastomoses in the subcutaneous tissues, or to valvular incompetence in the communicating veins (Ludbrook 1986). Several microcirculatory factors have also been implicated in the development of varicose veins (Burnand 1999).

Incompetence of the deep, superficial and/or perforating veins leads to an inability to reduce venous pressure during exercise, resulting in stasis of venous blood flow and raised pressure in the lower leg. This increased pressure leads to disturbances in the equilibrium between the inflow and outflow of the fluid in the interstitial spaces, which can result in interstitial oedema, inflammation and necrosis of the surrounding tissues (Krijnen et al. 1997a) with eventual venous ulceration.

1.4.3 Risk Factors

Secondary varicose veins develop due to underlying pathology, such as deep venous thrombosis or pelvic tumour (Burnand 1999). The risk factors for primary varicose veins are less well understood. Varicose veins are generally accepted as being more common in women than men and to increase in prevalence with age (Callam 1994). There is some evidence that pregnancy and obesity are risk factors for varicose veins

(Kurz et al. 1999). Other postulated risk factors include positive family history, prolonged standing, constipation, the wearing of tight undergarments, heavy lifting, lack of exercise and cigarette smoking. However, evidence from existing studies is variable and generally inconclusive (Kurz et al. 1999, Lee et al. 1999).

1.5 INVESTIGATION OF VENOUS DISEASE

This section will briefly describe the methods of assessment for venous disease. Duplex ultrasound was the method of measurement of venous function used in the Edinburgh Vein Study and a more detailed discussion of this method will follow in Section 1.5.4.

1.5.1 Initial assessment

Investigation of a patient with varicose veins involves history taking and clinical examination of the legs. This will reveal the severity of the patient's symptoms and whether they are likely to be attributable to venous disease or other pathology. Classic tourniquet tests may provide some information on the sites of deep to superficial reflux. A simple doppler probe can be used to detect reflux at the saphenofemoral and saphenopopliteal junctions, and is routinely used in outpatient clinics (Nicolaidis 1999). Special investigations can then be employed if these simple measures are inconclusive (Hobbs 1991).

1.5.2 Invasive tests

Phlebography

Phlebography was the main method of imaging in patients with recurrent varicose veins and CVI prior to the development of Doppler ultrasound techniques (Allan 1999). It allows visualisation of obstruction, old thrombus, recanalisation and collateral circulation. Ascending phlebography illustrates the anatomy while descending phlebography demonstrates the extent and location of reflux and provides information on the venous valves (Nicolaidis 1999). Varicography involves injecting contrast medium directly into the varicose veins and following the channels the contrast takes to join the deep system or the groin and perineum (Allan 1999). However phlebography is an invasive and expensive procedure and in most cases has been replaced by duplex scanning (Nicolaidis 1999).

Ambulatory venous pressure measurements

As well as visualising the anatomy, methods to assess the venous function of the limb may be required. Ambulatory venous pressure (AVP) measurements detect the venous pressure directly. A needle is inserted into a superficial vein in the foot and connected to a strain gauge. Venous pressure decreases in the foot during exercise as the calf muscle expels venous blood. On ceasing exercise, the pressure gradually recovers to the resting value as the veins refill. When there is extensive valve failure in either the deep or superficial veins, the pressure fall during exercise is less and the recovery time is shorter. If temporary occlusion of the superficial veins fails to lengthen recovery time, it is likely that the defect lies in the deep veins (Tibbs 1992). Because AVP testing is invasive, it cannot be used for screening. However, the

method remains the gold standard for haemodynamic function against which other non-invasive tests are validated (Nicolaidis 1999).

1.5.3 Plethysmography

Plethysmography refers to the recording of changes in the size of a limb. Instead of directly measuring the pressure changes during and after exercise, plethysmographic techniques measure changes in volume which occur in the limb (Tibbs 1992). Different types of plethysmography are briefly described below.

- Foot volumetry involves the patient standing in a temperature-controlled water bath and performing knee bends. Measurement of the fluid displacement in the water bath corresponds to the volume changes in the limb (Browse et al. 1988).
- Impedance plethysmography measures the change in tissue electrical resistance associated with a change in the volume of blood in the limb (Browse et al. 1988). The electrical resistance rises as the bulk of the limb increases with inflow of blood (Tibbs 1992).
- In strain gauge plethysmography an electronic strain gauge is placed around the calf. A change in volume of the calf causes a change in the length of the gauge which leads to a change in resistance of the fluid conductor contained within the gauge (Browse et al 1988, Tibbs 1992).
- Photoplethysmography measures the reflectivity of the skin via an infra-red light source and a photoelectric detector (Browse et al. 1988). Light is absorbed by haemoglobin in red blood cells. The higher the venous pressure in the leg, the more the skin capillaries become distended and filled with blood, and the more

light is absorbed (Tibbs 1992). Light refraction rheography and digital photoplethysmography have evolved from photoplethysmography and incorporate computer technology to allow measurements of time-related parameters and amplitude (Nicolaidis 1999).

- Air phlethysmography involves enclosing the leg in an air chamber and observing pressure changes (Nicolaidis and Christopoulos 1991). The method allows evaluation of the individual components of venous hypertension namely reflux, outflow obstruction and the performance of the calf muscle pump. It provides information on the venous function of the whole leg, whereas duplex scanning detects abnormalities in individual veins (Nicolaidis 1999).

1.5.4 Diagnostic Ultrasound

The role of ultrasound has been developed over recent years, contributing to increased understanding of the pathophysiology of venous disorders (Allan 1999).

The principles of ultrasound and the use of this technique in assessing venous incompetence will now be considered.

Principles

Ultrasound refers to any sound wave of frequency higher than 20 KHz which cannot be heard by the human ear. In a diagnostic ultrasound machine, a transducer containing piezoelectric crystals emits high frequency sound waves, between 1 and 15 MHz, by application of an electric current. When the ultrasound beam is transmitted into the body, sound waves are absorbed, attenuated or reflected to different degrees by the tissues, with soft tissues being poorly echogenic and bone and tissue boundaries producing strong echoes. Reflected sound waves are received by transducer crystals and converted into electric signals. The amplitude of the reflected ultrasound, and the time the signal has taken to travel from the transmitting to the receiving crystal, allow a detailed image to be constructed in differing shades of brightness (brightness modulation or B-mode ultrasound) (Browse et al. 1988, Massoud and Shepstone 1992).

Doppler ultrasound can be used to detect blood flow in a vessel. The technique depends on the principle that 'the frequency of a sound wave reflected from a moving object is changed in proportion to the speed of movement of the reflecting object' (Massoud and Shepstone 1992). Sound is reflected back at a lower frequency from an object moving away from the source of the sound, while an object moving towards the source reflects sound at an increased frequency. The change in the frequency of the reflected sound can be used to detect and measure the velocity of movement of the object. To measure blood flow through a vessel, the probe is coupled to the tissues using jelly to prevent all the sound being reflected at the air-skin interface. The ultrasound is directed towards a blood vessel and sound waves are reflected from

the red blood cells. Movement of the red cells is indicated by a change in the reflected frequency of the sound waves (Browse et al. 1988, Massoud and Shepstone 1992).

Use of duplex scanning to detect venous reflux

Duplex ultrasound scanning combines B-mode ultrasound imaging with pulsed Doppler to provide anatomical and functional information on blood flow. Specific veins can be identified and the presence, direction and velocity of blood flow at different locations within the vessel can then be established. The more recently developed Doppler systems enable the moving blood to be represented as a colour; the colour is dependent on the direction of the blood flow in relation to the transducer and the tone represents the velocity of the blood flow (Allan 1999). Colour systems have the advantages of rapid identification of the veins and the ability to visualise the blood flow and venous reflux in the veins directly (Massoud and Shepstone 1992).

Duplex scanning has become the method of choice for the investigation of venous reflux (Labropoulos et al. 1994a) and a standard against which to judge other investigations of venous disease (Thibault 1995). A recent Consensus Committee formed to develop standards for reporting of venous disease, considered duplex ultrasonography to be the 'best-documented non-invasive method of quantifying reflux by measuring reflux duration' (Porter et al. 1995). Duplex scanning has been shown to reflect the degree and distribution of reflux, as correlated to clinical severity of disease, more accurately than descending phlebography (Neglen and Raju 1992) and to correlate better with foot volumetry than descending phlebography in the

evaluation of deep venous reflux (Baker et al. 1993). When compared to ambulatory venous pressure measurements, the sensitivity and specificity of duplex scanning in detecting deep venous incompetence has been shown to be 84% and 88% respectively (Szendro et al 1986). When used to identify patients with moderate to severe CVI, the sensitivity and specificity of a multiple-segment scoring system derived from reflux observed in different vein segments, was 83% and 86% respectively (Neglen and Raju 1993). However, another study found that measurement of reflux time in different vein segments was not consistent in distinguishing between different categories of severity of disease (Valentin and Valentin 1999). A further study concluded that although measuring duration of reflux was a useful method for determining the presence of reflux, it did not correlate with the magnitude of reflux and should not be used to quantify the degree of reflux (Rodriguez et al. 1996). The repeatability of duplex scanning for the measurement of venous reflux in patients with severe venous disease was examined in a recent study. The inter- and intra-observer reproducibility was found to be reasonable at certain sites but appeared to be influenced by the position of the vein and by observer training and experience (Evans et al. 1995).

The use of duplex scanning in epidemiological studies

Duplex scanning is acceptable for use in epidemiological studies as it is non-invasive and painless, and considered to be safe. However, the equipment is expensive, the examination time-consuming and reliant on a well-trained operator. Epidemiological studies frequently require several observers taking measurements over a long study period, emphasising the importance of measures to reduce observer variability, such

as the development of detailed study protocols, adequate initial training for observers and regular monitoring of performance (Evans et al. 1995).

1.6 THE EDINBURGH VEIN STUDY

1.6.1 Context

Despite venous disease being a common and costly condition, there has been relatively little population-based epidemiological research conducted in this area. Many existing studies have examined specific populations such as clinic patients or occupational groups, limiting the extent to which the findings can be extrapolated to the general population. The Edinburgh Vein Study is the first large scale study of its kind to investigate the prevalence of venous disease in the general population, using duplex ultrasound scanning to measure venous function.

1.6.2 Aims and objectives of Edinburgh Vein Study

The overall aims of the Edinburgh Vein Study were to determine the extent of venous disease in the general population and to identify associated genetic and lifestyle risk factors, with the long term view of establishing measures for prevention. More specifically, the study aimed:-

- to determine the prevalence of varicose veins, CVI and venous reflux on duplex scanning in a random sample of the general population.
- to determine the association between these manifestations of venous disease and various genetic and lifestyle factors.
- to establish a cohort of men and women in the general population as a basis for future studies to examine:-
 - the incidence and natural history of venous disease.
 - the genetic heritability of venous disease.

1.7 THESIS

1.7.1 Objectives of thesis

This thesis presents some of the results from Edinburgh Vein Study. The specific objectives to be addressed in the thesis are as follows:-

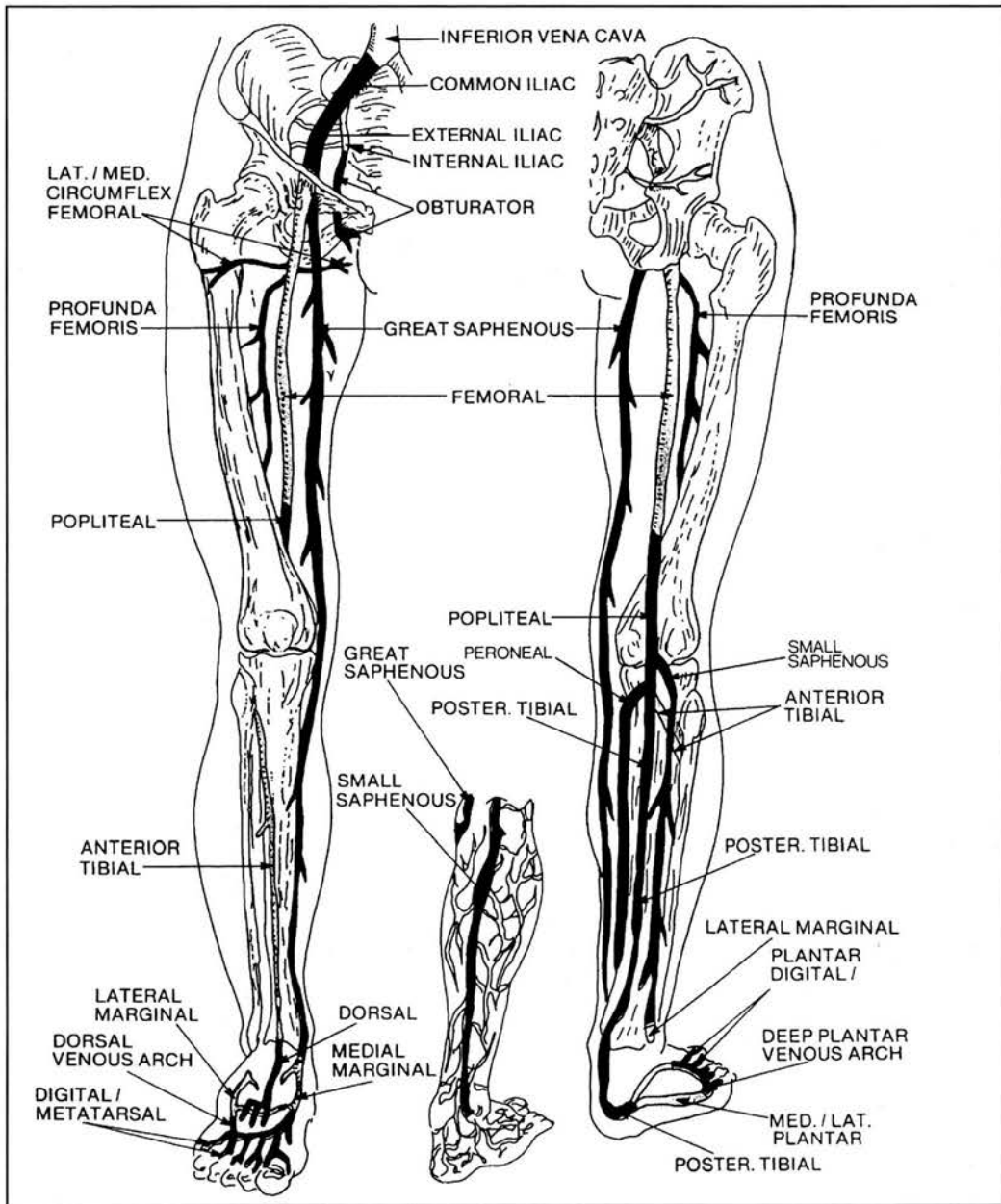
1. To determine the prevalence of varicose veins and CVI in men and women in the Edinburgh Vein Study population by:-
 - age and sex.
 - side of the body.

- social class and deprivation.
 - body mass index.
2. To determine the prevalence of previous treatment for varicose veins in men and women.
 3. To assess the study methods used by comparing results obtained from:-
 - different methods of measurement.
 - different observers.
 4. To estimate the prevalence of varicose veins in the total study population, using results from a follow-up survey of a proportion of the non-responders.
 5. To determine the prevalence of venous reflux ≥ 0.5 seconds and > 1.0 second in individual vein segments in the study population.
 6. To examine the prevalence of venous reflux according to age and sex.
 7. To examine the patterns of venous reflux in deep and superficial vein segments.
 8. To examine the relationship between the presence or absence of 'venous disease' and:-
 - the prevalence of reflux.
 - the distribution and duration of reflux.
 9. To explore the cut-off point for 'significant' duration of reflux.
 10. To examine the relationship between severity of venous disease and presence of reflux.

1.7.2 Format of thesis

The thesis will address the objectives listed in Section 1.7.1 above. The report will begin with an overview of the prevalence of venous disease from the available literature. The methods used in the Edinburgh Vein Study will then be described. Results from the study will be presented focussing on the response rate and characteristics of the study population, the prevalence of venous disease on clinical examination and the prevalence of venous reflux on duplex scanning. These findings and their implications for public health will be discussed. Finally conclusions will be drawn and recommendations for future research proposed. Tables and figures will be presented at the end of each chapter in the order in which they are referred to in the text.

Figure 1.1 Venous system of the lower limb

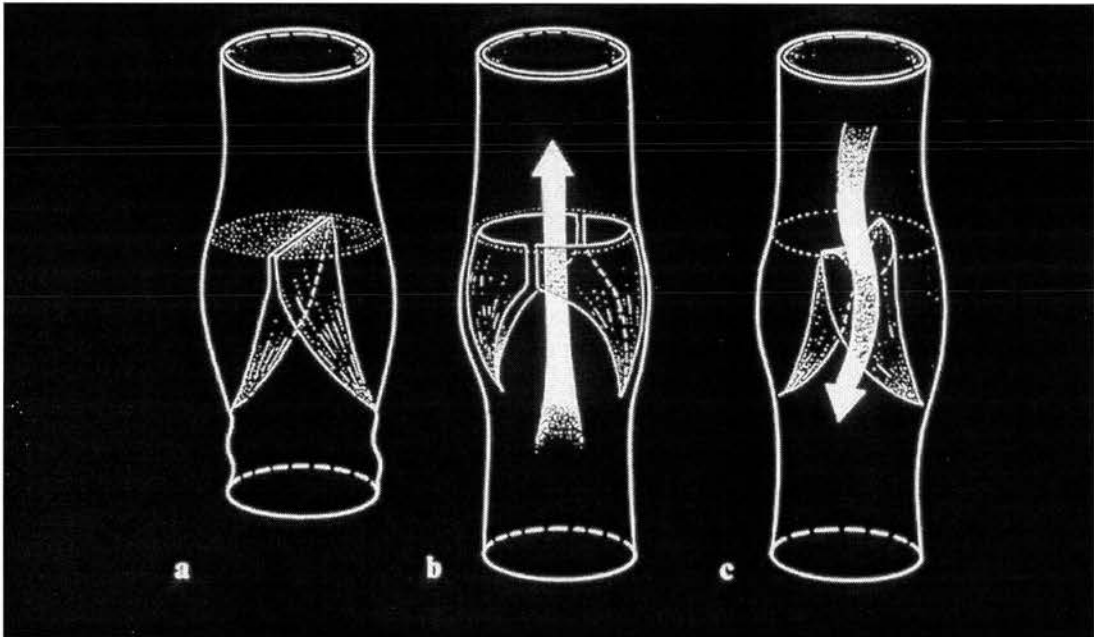


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Footnote:

- Great saphenous vein is equivalent to long saphenous vein (LSV)
- Small saphenous vein is equivalent to short saphenous vein (SSV)
- 'Femoral vein' is frequently subdivided into the terms 'superficial femoral vein' (SFV) distal to the confluence with profunda femoris vein and 'common femoral vein' (CFV) proximal to this point

Figure 1.2 Diagram of a venous valve
(Adapted from Tibbs 1992)



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Footnote:

(a) Competent valve in a closed position with cusps fully opposed

(b) Upward flow through an open valve

(c) Incompetent valve in a closed position with cusps incompletely opposed allowing some reverse flow

CHAPTER 2

PREVALENCE OF VARICOSE VEINS AND

SKIN CHANGES OF CHRONIC VENOUS INSUFFICIENCY -

A LITERATURE REVIEW

2.1 INTRODUCTION

Many studies of venous disease have focussed purely on the most severe end of the spectrum; the point prevalence of open venous leg ulceration is estimated to be 0.08-0.1% for the whole adult population, increasing markedly in the older age groups (Callam 1999). However, this thesis is principally concerned with the occurrence of conditions prior to the development of venous ulceration, namely varicose veins and skin changes of CVI. This chapter reviews the available evidence from the literature on these conditions, with reference to the methodological differences between existing studies and variation in prevalence according to age, sex and geographical and racial factors.

2.2 VARICOSE VEINS

2.2.1 Methodological issues

Attempts have been made recently to standardise the reporting of venous disease, with the development of the 'CEAP' classification of chronic venous disease (Porter

et al. 1995). In addition, non-invasive methods of measurement such as Doppler and duplex ultrasound have become widely available and now offer objective methods of assessment of venous function acceptable for use in epidemiological studies. However, most of the studies providing data on the incidence and prevalence of varicose veins have not used such objective methods or standardised classification systems. Comparison of results from these studies is difficult due to variations in the methods and definitions used. Furthermore, many existing studies have examined selected population groups and the generalisability of results from such groups is questionable. These methodological issues will now be considered in further detail.

Definitions

An International Consensus Committee on Chronic Venous Disease recently designed the CEAP classification of venous disease, which is based on clinical signs (C) (Table 2.1(a)), cause (E for etiology), anatomic distribution (A) and pathophysiologic condition (P) (Porter et al. 1995). Table 2.1(b) shows recently agreed definitions for degrees of venous dilation used in this classification. Prior to the development of these guidelines, several investigators used the definition of Arnoldi for varicose veins (1957 and 1958) 'any dilated, tortuous and elongated subcutaneous veins of the lower leg' (Beaglehole et al. 1975, 1976, Hirai et al. 1990, Komsuoglu et al. 1994, Maffei et al. 1986, Malhotra 1972, Stanhope 1975). In the Framingham Study varicose veins were defined as 'the presence of distended and tortuous veins, clearly visible in the lower limbs with the subject standing' (Brand et al. 1988) and a similar definition was used by Abramson et al. (1981) in a community survey in Jerusalem. In the Tecumseh Community Health Study, the

diagnosis of 'any varicose veins' included 'all subjects in whom prominent superficial veins were noted in the lower extremities' (Coon et al. 1973), which was similar to definitions used later in studies in Sicily and Czechoslovakia (Novo et al. 1988, Stvrtinova et al. 1991). In a study of hereditary factors in venous insufficiency, Gundersen and Hauge (1969) used a World Health Organisation definition for varicose veins 'saccular dilation of the veins which are often tortuous'. Mekky et al. (1969) used the definition of Dodd and Cockett (1956) 'A varicose veins is one which has permanently lost its valvular efficiency... as a result of continuous dilation under pressure, in the course of time a varicose vein becomes elongated, tortuous, pouched, thickened.'

An important variation in definitions used is the inclusion (Da Silva et al. 1974, Hirai et al. 1990, Komsuoglu et al. 1994, Novo et al. 1988, Stvrtinova et al. 1991) or specific exclusion (Abramson et al. 1981, Brand et al. 1988, Gundersen and Hauge 1969, Laurikka et al. 1993, Mekky et al. 1969) of abnormalities of the venules, (hyphenwebs/telangiectasias) and of mild reticular varices (Guberan et al. 1973, Maffei et al. 1986). This variation will have contributed to marked differences in the overall prevalence of varicose veins reported in these studies. In the Basle Study (Widmer 1978) varicose veins were divided into three categories, each graded 1-3 according to 'the degree and extent of tortuosity and prominence' (Table 2.2). Other studies have also reported different grades of severity of varices (Beaglehole et al. 1976, Coon et al. 1973, Da Silva et al. 1974, Ducimetiere et al. 1981, Latta et al. 1973, Maffei et al. 1976, Prior et al. 1970, Stanhope 1975). The gradings were often arbitrary, and varied between studies, but reflected an attempt to distinguish between

medically significant and insignificant varicose veins. In a pilot survey, Weddell (1969) defined 'clinical' and 'non-clinical' varicose veins by an association of signs with symptoms. In the Basle Study, a distinction was made between subjects with venous 'disorder' and 'disease', based on a statistical correlation between type and degree of varicosity and CVI (Madar et al. 1986, Widmer 1978).

Methods of measurement

Many studies have used both history and examination to assess the presence of varicose veins. While some studies have made use of questionnaires to standardise history taking (Coon et al. 1973, Maffei et al. 1986, Malhotra 1972, Mekky et al. 1969, Schultz-Ehrenberg et al. 1992, Stvrtinova et al. 1991, Weddell 1966), two recent studies from England and Finland have used postal questionnaires exclusively to investigate the prevalence of varicose veins in general population samples (Franks et al. 1992, Laurikka et al. 1993). While being easier and cheaper to administer than physical examination of subjects, such questionnaires rely on self-reporting of varicose veins which may be unreliable. In the English study, comparison of results from the questionnaire with examination findings for a self-selected group of subjects, revealed a sensitivity of 76% and a specificity of 86% for the questionnaire (Franks et al. 1992). In the Finnish study, the sensitivity and specificity of the questionnaire was 92% and 91% respectively in women, and 93% for both parameters in men, when results were compared to evaluation by a surgeon, although self-assessed diagnosis was shown to be less accurate in those with a familial predisposition to varicosis (Laurikka et al. 1995).

Sisto et al. (1995) used a questionnaire to determine the prevalence of diagnosis of varicose veins in the past by a physician but no validation of this method of assessment was performed. In a study from Czechoslovakia, only 56% of women working in a department store had themselves noticed the varicose veins which were diagnosed on examination (Stvrtinova et al. 1991). When the prevalence of varicose veins from interview data was compared with clinical examination data in a study from Israel, the sensitivity and specificity of interview was 47% and 95% in men and 67% and 85% in women respectively (Abramson et al. 1981). Hence the validity of questionnaires used in different studies was variable and was affected by the characteristics of the population being assessed.

Most studies have examined subjects in a standing position. Attempts to standardise the examination technique have included an initial supervised training period for the observers (Komsuoglu et al. 1994, Maffei et al. 1986), the use of only one observer (Malhotra 1972, Mekky et al. 1969) and joint classification by two observers (Latto et al. 1973). The problems of inter-observer variability were highlighted in a study of Paris policemen (Ducimetiere et al. 1981). Among results from the twelve examining physicians, who each saw at least 200 men in the study, the observed prevalence of varicose veins varied from 14% to 40%. In the Basle study, in addition to physical examination of the legs, 3 colour photographs were taken and reclassified by one or more observers at the end of each stage of the study to obtain a 'homogeneous classification'. In the Basle III study, the reproducibility of this method was shown to be 72-84% for different types of varicose veins and 73-87% for different grades (Widmer 1978).

A few recent studies have used more objective methods to measure venous insufficiency. The longitudinal Bochum Study used Doppler ultrasound to detect venous reflux in schoolchildren on three occasions during their education (Schultze-Ehrenberg et al. 1992). Stvrtinova et al. (1991) used Doppler ultrasound to assess patency and valvular function in the lower limbs of women working in a department store in Czechoslovakia. In the San Valentino Venous Disease Project, duplex scanning is being used to evaluate venous patency and incompetence, and light reflection rheography to calculate the venous refilling time in the lower limbs of the population of a village in central Italy (Cesarone et al. 1997).

2.2.2 Prevalence and incidence

Table 2.3 shows the prevalence of varicose veins observed on examination of subjects in studies from various countries. As discussed above, there was no uniform definition or method of measurement used in these studies. The age and sex distributions of the populations examined also varied widely. One study sample comprised men and women randomly selected from the general population (Leipnitz et al. 1989) while others were made up of selected occupational groups of only one sex (Ducimetiere et al. 1981, Guberan et al. 1973, Malhotra 1972, Mekky et al. 1969, Stvrtinova et al. 1991), or of hospital or clinic patients (Maffei et al. 1986, Richardson and Dixon 1977). Given these reservations, the prevalence of varicose veins in these studies varied widely from 0.1% in women from villages in rural New Guinea (Stanhope 1975) to 60.5% in women working in a department store in Czechoslovakia (Stvrtinova et al. 1991).

The classification used in the Basle Study differentiated reticular and hyphenweb varices from trunk varices (Table 2.2) (Widmer 1978). When all types and severity of varices were included, 56% of men and 55% of women from the chemical industry in the Basle III study had varices. Trunk varicosity occurred in 20% of men and 11% of women, being combined with hyphenweb and/or reticular varices in the majority of cases. Hyphenweb and/or reticular varices were approximately three and four times more common than trunk varices in men and women respectively, and were present in the absence of trunks in 36% of men and 44% of women. In a study of Japanese women aged 15-90 years, reticular varices were present in 58% and hyphenweb varices in 61% of women (Hirai et al. 1990). Stvrtinova et al. (1991) examined 696 women working in a department store in Czechoslovakia and found a prevalence of 15.4% for reticular varices and 30.7% for hyphenwebs, in addition to the 14.4% of women who had trunk varices.

The incidence of varicose veins refers to the development of new cases over a period of time in a population initially free of disease. The longitudinal Framingham Study followed up men and women who were living in the town of Framingham, USA (Brand et al. 1988). Every two years, over a 16 year period from 1966 onwards, subjects were examined for varicose veins, defined as 'the presence of distended and tortuous veins, clearly visible on the lower limbs with the subject standing'. Abnormalities of the venules were excluded. Over the 16 year period, 396 out of 1720 men and 629 out of 2102 women who were free from the condition in 1966, developed varicose veins. The two-year incidence of varicose veins was on average 39.4 per 1000 for men and 51.9 per 1000 for women. The Bochum Study examined

schoolchildren on three occasions during their education (Schultz-Ehrenberg et al. 1992). At the first examination, none of the children (aged 10-12 years) exhibited varices of the trunk veins or their tributaries, although there was already venous reflux present in the long and short saphenous veins in 2.5% of children on Doppler examination. By age 14-16 years, 1.7% of the children had trunk varices and 0.8% varices of the tributary veins while 12.3% showed saphenous reflux. These figures increased to 3.3% and 5.0% for varices of trunk and tributary veins respectively by age 18-20 years, with a prevalence of 19.8% for saphenous reflux on Doppler examination. The prevalence of reticular varices increased from 10.7% at the first examination to 35.3% by the third examination. The only other available data on incidence is in an unpublished paper from the Basle Study, which described an 11 year follow-up of a subgroup from this study population (Widmer et al. 1992). In 660 subjects initially free from varicose veins, 87% developed mild and 5% pronounced varicose veins over the 11 year period. Further studies are required to determine the incidence and progression of venous disease in the general population. One such study is the San Valentino Venous Diseases Project. This study was initiated in July 1994, with the aim of evaluating the prevalence of venous diseases in the population the village of San Valentino, central Italy, and following the progression over a period of ten years (Cesarone et al. 1997).

2.2.3 Sex differences

Most studies have found a higher prevalence of varicose veins in women compared to men (Table 2.3). However, it has been suggested that the sex ratio decreases with increasing age (Beaglehole 1986). Furthermore, many of the results from existing

studies have not been adjusted for differences in age between the men and women in the study population, a factor which may have contributed to the observed sex differences (Richardson and Dixon 1977). Differences in the prevalence of venous disease between men and women will be discussed further in Chapter 7.

2.2.4 Effects of age

A common finding in most studies is that the prevalence of varicose veins increases with increasing age. Figure 2.1(a) shows the increase in prevalence of varices with age in women from three surveys (Abramson et al. 1981, Guberan et al. 1973, Mekky et al. 1969). In the longitudinal study of Bochum schoolchildren described above, the prevalence of both varices and venous reflux increased with age (Schultz-Ehrenberg et al. 1992).

In the Framingham Study, which examined a population biannually over a 16 year period for the presence of varicose veins, the incidence of varicose veins did not increase with age (Brand et al. 1988). The observed increase in the prevalence of varicose veins with age would therefore appear to be a result of the continuing accumulation of cases as people grow older.

2.2.5 Geographical and racial differences

There is much anecdotal evidence in journal correspondence from those working in the developing world in the 1960's and 1970's to suggest that the prevalence of varicose veins is lower in these countries than in the Western world (Coles 1974,

Milton-Thomson 1974, Williams 1974, Worsfold 1974). Barker (1964) reported only 2 cases of varicose veins out of a total of 3000 hospital patients in a Zulu area of Africa. In a letter reporting on several case series of hospital patients in India, Burkitt et al. (1975) concluded that the prevalence of varicose veins in rural Indians was unlikely to exceed 2%. In Mombasa, Kenya, 294 pregnant women from different racial groups were examined for varicose veins (Burkitt et al. 1976). The prevalence of varices was 1.5% in Arab women, 3.2% in African women and 9.7% in Indian women. A survey of 2084 hospital patients in Peru revealed only 3 cases of varicose veins (Dalrymple and Crofts 1975) while Richardson and Dixon (1977) reported that 5.5% of Tanzanian outpatients had varices (Table 2.3).

While the above reports were based on hospital populations, others attempted to survey a wider population. Rougemont (1973) examined all women from 10 traditional villages in the Republic of Mali using 'well-standardised criteria and methods' and found an overall prevalence of 10.9% for all types of varicose veins, 4.5% of which were severe. Despite a higher than expected prevalence, none of these cases were associated with complications. Daynes and Beighton (1973) examined 297 women aged 18 years and over in the Transkei, Southern Africa and found varicosity of the main leg veins in 7.7%, the prevalence rising with age. However, none of the women complained of any associated symptoms. Rivlin (1974) believed that there was an equal prevalence of varicose veins throughout the world but that the occurrence of symptoms and complications was virtually unknown in tropical Africa. Hence conflicting anecdotal accounts and a lack of well designed epidemiological

studies make it difficult to draw any conclusions about the true prevalence of varicose veins in underdeveloped countries.

A few studies have compared prevalence of varicose veins in different racial groups. In a community study in Jerusalem, Abramson et al. (1981) found a lower prevalence of varicose veins in immigrants over 45 years of age from North Africa (men 13.2%, women 30.2%) compared to immigrants from Europe and America (men 26.9%, women 48.8%) and other parts of Asia (men 22.4%, women 39.7%). Guberan et al. (1973) found the prevalence of varices significantly lower among women from Southern Europe (Italy and Spain) than among the other women in their study from Switzerland, France and other Central European countries. In a study of women cotton workers, the prevalence of varicose veins was 32% among European women compared to 6% among Egyptian women (Mekky et al. 1969). Beaglehole et al. (1975) examined the prevalence of varicose veins in several contrasting South Pacific populations. There was a gradient in the prevalence of varices which followed the pattern of contact of the populations with the Western world, being lowest in the Atoll dwellers (Tokelau Islanders and Pukapukans), intermediate in the Rarotongans and highest in the New Zealanders (European and Maori groups) (Table 2.3).

2.3 SKIN CHANGES OF CHRONIC VENOUS INSUFFICIENCY

Only a few studies have investigated the occurrence of skin changes of CVI, usually during the course of an investigation into the prevalence of varicose veins. Data on

skin changes of CVI will be considered separately for (i) samples of the population and (ii) patients with varicose veins.

2.3.1 Prevalence in different types of population sample

Table 2.4 shows the prevalence of skin changes of CVI for different types of population samples. As with studies of varicose veins, the definitions used and the age and sex composition of the populations varied between the studies, making direct comparison difficult. In a study from Klatov, Czechoslovakia, by Bobek et al. (1966) questionnaires were given to all inhabitants of a district over 15 years of age. Those who mentioned any venous problems were examined by a local doctor, and all apart from those with minimal varicosities and no complications were examined by the study team. Signs of venous insufficiency such as oedema or trophic problems were present in 3.4% of women and 1.9% of men. The Tecumseh community health study was a longitudinal study of a total community in the USA (Coon et al. 1973). The presence of stasis skin changes was recorded if increased pigmentation, fibrosis, induration or atrophy of skin at or adjacent to the medial malleolus was present at the time of examination. The overall crude prevalence of such changes was 3.0% for men and 3.7% for women. However, the prevalence increased with age in both sexes, and the age-specific rates were generally similar for men and women, as illustrated in Figure 2.1(b). In addition to these general population surveys, a recent unpublished study from South Wales examined a randomly selected sample of 560 men and women over 60 years of age. The prevalence of signs associated with CVI of all degrees (including active or healed ulceration) was 29.2% and was significantly higher for women than for men (I Harvey, personal communication).

Two studies have investigated the prevalence of skin changes of CVI in working populations (Table 2.4). In the Basle Study, workers from the chemical industry in Switzerland were examined for the presence of varicose veins and CVI according to the definitions in Table 2.2 (Widmer 1978). The prevalence of CVI 2, defined as hyper- or depigmented areas with or without a venous flare, was 6% in men and 5% in women. Once again, the prevalence increased with age in both sexes. Krijnen et al. (1997b) examined European males in the Netherlands who had a standing position at work (defined as standing for more than 80% of working time on approximately 1m²) for the presence of CVI. The prevalence of minor CVI (venous flare, (Basle Study grade 1 CVI), subclinical oedema or side branch varicosis) was 18% and major CVI (skin changes (Basle Study grade 2/3 CVI) or signs of deep venous insufficiency or stem varicosis) was 11%, both higher than in the Basle Study population. The prevalence of CVI increased from 10% in those under 25 years to 60% in those over 55 years of age.

2.3.2 Prevalence in patients with varicose veins

Several studies have reported the prevalence of CVI in subjects who have varicose veins. In a pilot study, Weddell (1966) examined a randomly selected sample of 88 subjects from the general population and 201 of their first degree relatives. While an ankle flare was seen in 40% of men and 19% of women without varicose veins or any signs of venous insufficiency, 'the signs of oedema, induration, pigmentation, eczema and varicose ulcer are significantly more common in those with varicose veins than in those without'. In the Basle Study, the prevalence of CVI in subjects with trunk varices was found to be 27% compared to 0.5% in those with no trunk

varices (Widmer 1978). When adjusted for the age difference between these two groups, the prevalence of CVI in subjects with trunk varices was 11 times more prevalent than in subjects without trunks.

Mekky et al. (1969) compared the prevalence of venous disease in women working in the cotton industry in England (mostly Europeans) and Egypt. Of the 162 European women with varicose veins, 52 (32.1%) had complications such as pigmentation, varicose ulcer, oedema and eczema, while none of the Egyptian women had complications. In a study of Indian railroad workers, 2.5% of South Indian workers had similar signs of CVI (Malhotra 1972). In a study of 1755 clinic patients in Botucatu, Brazil, oedema was found in 19.7%, hyperpigmentation in 5.7%, eczema in 1.4% and skin fibrosis in 0.6% of subjects with varicose veins but without active or healed ulcers (Maffei et al. 1986). In a study of residents over the age of 60 years from a county in Turkey, hyperpigmentation was found in 2.3% and eczema in 1.3% of those with varicose veins but without active ulceration (Komsuoglu et al. 1994).

2.4 SUMMARY

The prevalence of varicose veins and skin changes of CVI in the general population is difficult to determine due to a lack of epidemiological data in this area. Comparison of results from existing studies is complicated by the variations in methodologies and definitions used and generalisability of results is further hampered by a lack of data on random population studies. Many studies have found a higher prevalence of varices and CVI in women than men, although differences in

age between the sexes have not always been adjusted for in these studies, which obscures the picture. A common finding is that the prevalence of varices and CVI increases with age. However, the limited evidence available on the incidence of varicose veins suggests that this remains relatively constant across the age ranges. Anecdotal evidence suggests that varicose veins may be less common, with fewer complications, in developing countries and a few studies have found variations in prevalence according to racial group. However, there is a lack of good quality data comparing occurrence according to geographical and racial factors.

Table 2.1 The 'CEAP classification' definitions (Porter et al. 1995)

(a) Clinical classification of chronic lower extremity venous diseases

Term	Definition
Class 0	No visible or palpable signs of venous disease
Class 1	Telangiectases, reticular veins, malleolar flare
Class 2	Varicose veins
Class 3	Oedema without skin changes
Class 4	Skin changes ascribed to venous disease (eg. pigmentation, venous eczema, lipodermatosclerosis)
Class 5	Skin changes as defined above with healed ulceration
Class 6	Skin changes as defined above with active ulceration

(b) Definitions of venous dilation

Varicose veins	dilated, palpable subcutaneous veins generally larger than 4mm
Reticular veins	dilated, nonpalpable subdermal veins 4mm in size or less
Telangiectases	dilated intradermal venules less than 1mm in size

Table 2.2 Definitions used in the Basle Study (Widmer 1978)

Term	Definition
^a Trunk varices	dilated, tortuous trunks of the saphena magna or parva (long or short saphenous) vein and their branches of the first or second order
^a Reticular varices	dilated, tortuous subcutaneous veins, not belonging to the main trunk or its major branches
^a Hyphenwebs	intradermal venectasis
CVI Grade 1	dilated subcutaneous veins, "corona phlebectatica"
CVI Grade 2	hyper- or de-pigmented areas, with or without "corona phlebectatica"
CVI Grade 3	open or healed ulcer cruris

Footnote:

- ^a graded 1-3 according to "the degree and extension of tortuosity and prominence"

Table 2.3 Prevalence of varicose veins by sex, from different studies

1st Author & Year	Country	Population (n)	Male (%)	Female (%)
Bobek 1966	Bohemia	15060	6.6	14.1
Mekky 1969	Egypt	467	-	5.8
	England	504	-	32.1
Malhotra 1972	India (south)	323	25.1	-
	India (north)	354	6.8	-
Guberan 1973	Switzerland	610	-	29.0
Beaglehole 1975	Cook Island (Pukapukans)	377	2.1	4.0
	Cook Island (Rarotongans)	417	15.6	14.9
	New Zealand (Maoris)	721	33.4	43.7
	New Zealand (Europeans)	356	19.6	37.8
	Tokelau Island	786	2.9	0.8
Stanhope 1975	New Guinea	1457	5.1	0.1
Richardson 1977	Tanzania	1000	6.1	5.0
Widmer 1978	Switzerland	4529	56.0	55.0
Ducimetiere 1981	France	7425	26.2	-
Maffei 1986	Brazil	1755	37.9	50.9
Novo 1988	Sicily	1122	19.3	46.2
Leipnitz 1989	Germany	2821	14.5	29.0
Hirai 1990	Japan	541	-	45.0
Stvrtinova 1991	Czechoslovakia	696	-	60.5
Komsuoglu 1994	Turkey	850	34.5	38.3

Figure 2.1(a) Prevalence of varicose veins in women by age, in studies from Israel, Switzerland and England (Calculated from Abramson et al. 1981, Guberan et al. 1973, Mekky et al. 1969)

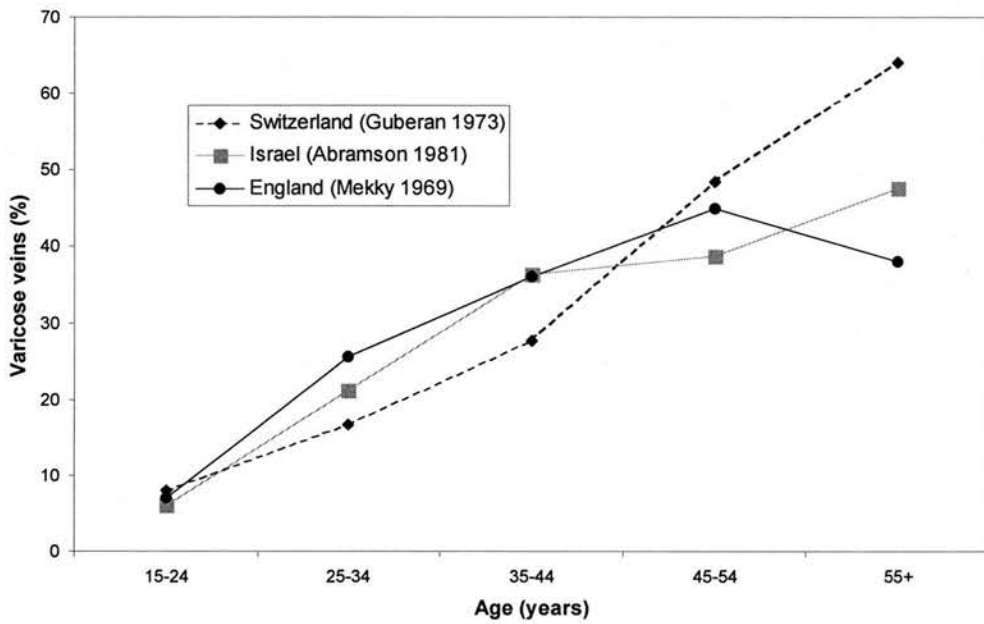


Figure 2.1(b) Prevalence of stasis skin changes by age, in the Tecumseh Community Health Study (Coon et al. 1973)

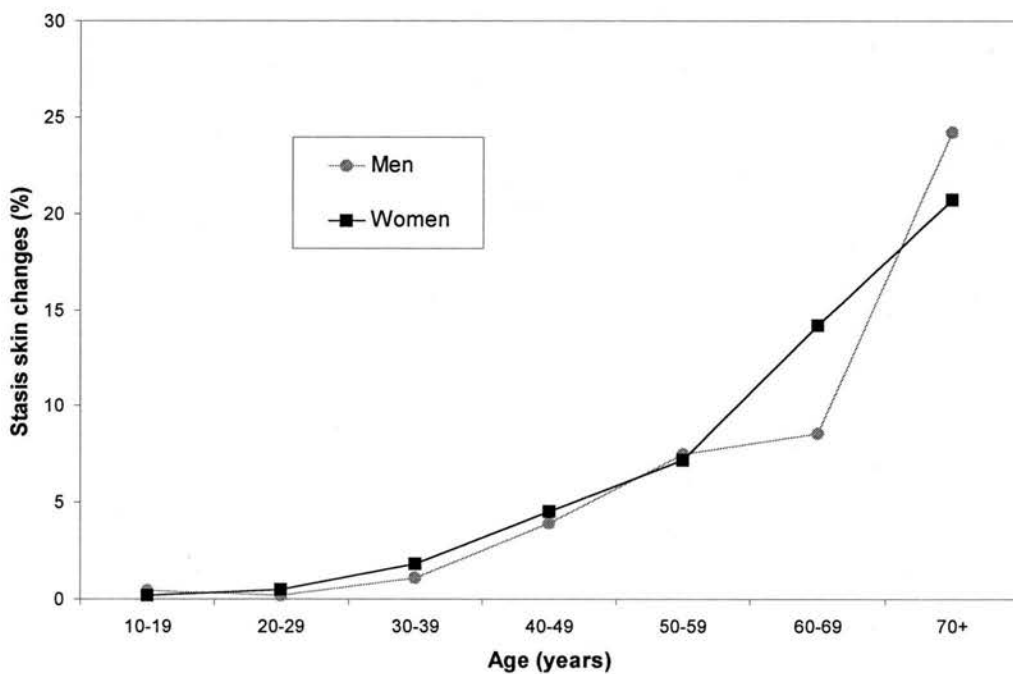


Table 2.4 Prevalence of skin changes of chronic venous insufficiency from different studies

1 st Author	Location	Population	Number by sex	Definition	Males (%)	Females (%)
Bobek 1966	Klatov, Czechoslovakia	General population >15 years	Males = 6540 Females = 8520	Oedema, trophic problems Leg ulcers	1.9	3.4
Coon 1973	Tecumseh, USA	General population >10 years	Males = 3026 Females = 3363	^a Stasis skin changes Varicose ulcer	3.0	3.7
Widmer 1978	Basle III Switzerland	Chemical industry employees	Males = 3744 Females = 785	^b CVI 1 – venous flare ^b CVI 2 – pigmentation change ^b CVI 3 – venous ulcer	9	7
Krijnen 1997b	Netherlands	Male workers with a standing profession	Males = 387	^c Minor CVI ^c Major CVI	18	-
					11	-

Footnote:

- ^aStasis skin change - increased pigmentation, fibrosis, induration, or atrophy of skin at or adjacent to the medial malleolus
- ^bSee Table 2.2 for full definitions
- ^cMinor CVI – venous flare, subclinical oedema or side branch varicosis
Major CVI – skin changes, signs of deep venous insufficiency or stem varicosis

CHAPTER 3

METHODS

3.1 INTRODUCTION

The Edinburgh Vein Study is the first large scale study in the United Kingdom to examine venous disease in the general population. The overall aim of the study was to determine the prevalence of varicose veins and CVI in a general population sample and to investigate the association between these conditions and certain genetic and lifestyle factors: the specific objectives of the study have already been discussed (Section 1.6.2). This chapter will describe the methods used in the Edinburgh Vein Study.

3.2 STUDY DESIGN

The study design was a cross-sectional survey of a random sample of the general population of Edinburgh. The initial study population will be followed up as a cohort.

3.3 STUDY POPULATION

3.3.1 Target population

The target population comprised inhabitants of Edinburgh aged 18 to 64 years of age.

3.3.2 Sample size

The primary outcome measure in the Edinburgh Vein Study was the prevalence of varicose veins. The sample size was estimated on the basis of the number required to detect a difference of 7% or greater in the prevalence of varicose veins between groups; for example 20% in women and 13% in men. It was calculated that approximately 1500 participants would be required to have 95% power at the 5% level of significance to detect a 7% difference in the prevalence of varicose veins between the sexes.

The calculation was as follows:-

$$\text{Number of subjects of each sex} = \frac{p_1(1 - p_1) + p_2(1 - p_2) \times f(\alpha, \beta)}{(p_2 - p_1)^2}$$

where

p_1 = the prevalence of varicose veins in the women.

p_2 = the prevalence of varicose veins in the men.

α = the type I error ie. the probability of detecting a significant difference in prevalence when both sexes have an equal prevalence (the risk of a false positive result).

β = the type II error ie. the probability of not detecting a significant difference in prevalence when there really is a difference in prevalence between the sexes (the risk of a false negative result).

$1 - \beta$ = the 'power' to detect a difference of magnitude $p_1 - p_2$.

In the Edinburgh Vein Study:-

$$p_1 = 0.20 \quad p_2 = 0.13 \quad \alpha = 0.05 \quad \beta = 0.05 \text{ (95\% power)}$$

$$\text{Number of subjects of each sex} = \frac{(20 \times 80) + (13 \times 87) \times 13}{(87 - 80)^2}$$

$$= 725$$

If an approximate prevalence of 20% is assumed for varicose veins then 1600 subjects will give a precision of +/- 2% for the prevalence. The calculation was as follows:-

$$\text{Number of subjects in study} = \frac{p(1-p)}{se^2}$$

where

p = the prevalence of varicose veins.

se = standard error of the prevalence (ie. the precision divided by two).

In the Edinburgh Vein Study:-

$$p = 0.20 \quad se = 0.01$$

$$\begin{aligned} \text{Number of subjects in study} &= \frac{0.20(1-0.20)}{(0.01)^2} \\ &= 1600 \end{aligned}$$

3.3.3 Sample recruitment

Twelve general practices participated in the Edinburgh Vein Study (Figure 3.1). Eleven of these practices had previously collaborated with the research group in an epidemiological study of peripheral arterial disease (Fowkes et al. 1991) and one practice was newly recruited for the Edinburgh Vein Study. They were distributed geographically and socio-economically throughout the city of Edinburgh and each practice had a computerised system of record keeping, nine of them using the GPASS system and three the MEDITEL system. The computerised age-sex registers were

stratified into 10 year age bands for each sex, and random sampling was carried out within each age-sex group, using a computer programme specifically designed for this purpose. Three hundred names were sampled from the first two participating practices. However, it became apparent during recruitment that more people would need to be approached in order to reach the target of 1500 participants. Therefore 450 names were subsequently sampled from practices 3 to 11 and 600 names from the final practice (Table 3.1).

The general practitioners reviewed the randomly selected lists of patients and excluded any whom they considered it was inappropriate to approach (for example, those with terminal illness or severe dementia). From the remaining names in each age-sex group, a smaller final number was further randomly selected to be invited to participate (Table 3.1). Proportionately fewer names were selected from the youngest age group, which spanned seven rather than 10 years.

Following publicity in the local media, a letter of invitation, signed jointly by the clinical research fellow and the subject's general practitioner, was sent to each selected participant, inviting them to attend a research clinic at the university for an examination of their legs (Appendix 1). Travel expenses were offered and evening appointment times were available for those unable to attend during the day. A home visit was offered to those unable to attend the clinic due to eg. disability.

A minimum of three attempts were made to contact by telephone those subjects who did not respond to the invitation, where telephone numbers were available. For those

subjects not reached by telephone, a second letter of invitation was sent. Subjects whose letters were either returned by the Post Office or a subsequent occupier, or who had moved from the area, were counted as 'returns'. If a period of at least one month had elapsed after sending a second invitation and still no contact was made with a subject, they were deemed 'unreachable'. For each subject classified as a 'return' or an 'unreachable' from practices 1 to 11, an invitation was sent to another randomly-selected subject from the same age-sex group from the same practice, where sufficient names remained available in the relevant group. Only one cycle of such replacement invitations was performed for each practice (Figure 3.2). For practice 12, invitations were sent to a larger number of subjects in each age group in the first round, and no second round of replacement invitations was performed (Table 3.1).

On receipt of an affirmative reply, an appointment time, map, details of the examination (Appendix 2) and a questionnaire (Appendix 3) were sent. The week before their attendance, the subject was contacted by telephone or post to remind them of their appointment. Responders who did not attend their appointment were offered a further appointment, usually by telephone, up to a total of three appointments. Those who withdrew from the study or ultimately failed to attend after agreeing to participate, were counted as 'withdrawals'.

3.4 STUDY MEASUREMENTS

3.4.1 Clinical examinations

Clinical examinations were held at a research clinic at the University of Edinburgh on certain weekdays and evenings between May 1994 and April 1996. Two subjects were examined concurrently during each appointment period of one and a quarter hours by one or more members of the research team, which comprised a research nurse, a technician and a clinical research fellow. Following each subject's appointment, a report of the clinical findings was sent to their general practitioner (Appendix 4). Those subjects wishing more information on varicose veins were offered an advice leaflet produced by the Health Education Board for Scotland and referred back to their general practitioner. Nineteen subjects had a 'home visit' appointment due to their inability to attend the university clinic for medical or social reasons. All routine procedures were performed at the home visits, apart from the duplex scan. Local ethics committee approval was given for the study and informed consent was obtained from each study participant (Appendix 5).

The following information was collected for each subject:- questionnaire data, height and weight, leg clinical examination, leg photographs, and duplex ultrasound scan of leg veins (Appendix 6). In addition each subject had a venous blood sample taken. A bowel record form was completed during the three days following the appointment.

3.4.2 Questionnaire

A self-administered questionnaire was completed by the subjects (Appendix 3) and checked by a member of the study team at the appointment. Details were asked about current marital and occupational status. The occupation covering the longest period of the subject's life and that of their most recent partner/spouse or father was documented. Information was also obtained on standing, sitting, walking and lifting at work, past relevant medical history including details of any treatment for varicose veins, family history of venous disease, leg symptoms, smoking history and bowel habit. A dietary fibre questionnaire (Tinuviel Software, Warrington, UK) adapted from a validated MRC fibre questionnaire (Barasi et al. 1983) was completed, and an obstetric history was obtained for female subjects. In addition, the researcher documented subject's ethnic origin as one of the following:- White Caucasian, African, Indian, Chinese or other (to be specified).

3.4.3 Height and weight

Subjects had standing height measured once to the nearest 5mm without shoes, using a free-standing metal ruler on a heavy base. Weight, without shoes or outer clothes, was measured to the nearest 100g on a digital Soehnle scale. Body mass index (BMI) was calculated according to the equation :

$$\text{BMI} = \text{weight in kilograms} / (\text{height in metres})^2$$

The height measuring stick and weighing scales used throughout the study were periodically calibrated against another instrument.

3.4.4 Leg examination and photographs

The method of examination and classification of venous disease used in the Edinburgh Vein Study (Appendix 7) was adapted from the Basle Study (Widmer 1978). (The CEAP classification for chronic venous disease was not available at the time of design and start of recruitment in the Edinburgh Vein Study (Porter et al. 1995). During inspection of the legs, subjects stood on a raised platform with their feet in three standard positions: facing towards the examiner with heels together and forefeet spread apart, facing away from the examiner in a similar position and facing away from the examiner with feet parallel (Figure 3.3). They were asked to remain in a standing position for a minimum of two minutes in order to allow the blood to pool in their legs prior to classification of their veins. Any scars and notable findings on the legs were documented.

Varices were divided into three types, according to the Basle Study classification (Table 2.2); trunk varices (Figure 3.4), reticular varices and hyphenweb varices (Figure 3.5). Each of the three groups was sub-divided into grades of severity 1-3, determined according to the 'degree and extent of tortuosity and prominence of the veins' (Widmer 1978). These grades were determined with reference to photographs from the Basle Study. In practice, grade 1 trunks ranged from a small discrete visible or palpable length of dilated trunk vein to more obvious but not grossly dilated varicose veins; grade 2 trunks were more extensive and/or more grossly dilated trunk varices and grade 3 trunks were varices at the most severe end of the spectrum. An additional category called 'perforators' (soft lumps which reduced on pressure and disappeared on elevation of the leg) was included to allow the documentation of visible incompetent

perforating veins or blow-outs. The lack of sensitivity and specificity of this definition of perforators was recognised. However it was considered important to document such abnormalities in subjects with no trunk varices, to avoid subsequent misclassification when grouping the study population into those with 'venous disease' and 'no disease' (see below). Each subject was examined for presence of any pitting ankle oedema and assessed for CVI graded 1-3 as described in Table 2.2. The grades of CVI correspond to the CEAP clinical classification for chronic venous disease (Porter et al. 1995) as follows: grade 1 CVI corresponds to Class 1 (malleolar flare), grade 2 CVI corresponds to Class 4 (skin changes) (Figure 3.6) and grade 3 CVI corresponds to Classes 5 and 6 (healed or active ulceration).

For the purposes of description, subjects were divided according to venous disease status as follows; the group with 'no disease' comprised those subjects with no trunk varices, CVI, 'perforators' or history of varicose vein treatment, and a maximum of grade 1 hyphenweb and/or reticular varices; the group with 'venous disease' included all subjects with trunk varices and/or CVI.

As in the Basle Study (Widmer 1978), photographs of the legs were taken. Three standard photographs were taken with the subject in the examination positions described above, two facing away and one facing towards the camera (Figure 3.3). Any varicose vein operation scars were then marked with water soluble ink, and further photographs were taken to document these. A Nikon FM2 camera with a 50mm lens, flash, tripod and Ektachrome 200 colour slide film was used and positioned at a distance to allow visualisation of the leg from the foot to mid/upper thigh. For

identification purposes, each subject was photographed beside their unique five digit study number. The photographic slides were subsequently independently analysed by the two members of the study team who had not examined the subject in the clinic, and graded according to the classification system described above. If the classifications of the two observers viewing the slides differed by less than two grades in each category, discussion between these two observers achieved a consensus classification for each subject. If there was a difference of two or more grades in any one category, then these were referred to the Professor of Vascular Surgery who made the final decision. This process resulted in two independent classifications of the venous status of each subject:- one based on examination in the clinic, and the other on analysis of the photographic slides (Appendix 8).

Several measures were adopted before and during the study to limit observer variability. The clinical research fellow co-ordinating the Edinburgh Vein Study received training from one of the investigators from the Basle Study in the classification technique. The research nurse and technician, who were the principal observers, were subsequently trained together in the method of classification of varices and CVI by the clinical research fellow. All three research team members were involved for the duration of the study. The photographic slides of subjects' legs were analysed and discussed weekly throughout the study by all three members of the research team and reference photographs from the Basle Study were reviewed periodically as a reminder of the original standard.

3.4.5 Duplex scanning

The duplex scans were performed with a Dasonics VST duplex scanner (Dasonics Sonotron, Zug, Switzerland) using a 5.0 MHz linear array probe according to the study protocol (Appendix 9). Cephalad venous flow was induced using a pneumatic cuff placed around the calf (cuff width 10cm, length 50cm), which was rapidly inflated and deflated using an automatic cuff inflator (Oak Medical, Scunthorpe, UK) to mimic a hand squeeze. For those calves of a larger diameter, a longer cuff was used (cuff width 10cm, length 65cm). A pressure of approximately 110mmHg was used to inflate the cuffs. If this standard pressure did not produce a forward flow equivalent to a minimum standard doppler shift of 0.5 - 1.0 kHz in the vein segment under examination, then a manual squeeze of the calf was used to elicit augmentation of venous flow for examination of that vein segment. Occasionally a manual squeeze of the thigh was employed. The refill time between compressions was a minimum of approximately 5 seconds.

Prior to the duplex scan, information was documented on history of varicose vein operations, recurrent fainting or blackouts and current use of hypotensive drugs. Each subject was examined standing on a tilting couch (Akron Therapy Products Ltd. Ipswich, England) at an angle of 45°. A pilot study prior to the Edinburgh Vein Study observed that a significant number of young subjects felt faint while standing on a tilting couch in the near upright position for duplex examination. Therefore the 45° position was chosen to give subjects some support in an attempt to minimise fainting during the procedure, while allowing gravity to act on blood within the leg. Any subject who did feel faint at this angle was examined in the 30° head up position. For

examination of the thigh, subjects stood with their back to the couch with the leg to be examined everted and slightly bent at the knee, and the weight mainly on the opposite leg. For examination of the segments behind the knee, the subject stood facing the couch with the leg to be examined slightly bent at the knee and the weight mainly on the opposite leg.

Measurements were made in the following eight vein segments along the deep and superficial veins of both legs (Figure 3.7):- the common femoral vein (CFV) proximal to the sapheno-femoral junction; the superficial femoral vein a) approximately 2cm distal to the confluence with the profunda femoris vein (upper SFV) and b) in the lower third of the thigh (lower SFV); the popliteal vein a) above the knee crease (above knee popliteal) and b) below the knee crease (below knee popliteal); the long saphenous vein a) just distal to the sapheno-femoral junction (upper LSV) and b) in the lower third of the thigh (lower thigh LSV); the short saphenous vein just distal to the sapheno-popliteal junction (SSV). In addition, the presence of any dual superficial femoral veins was documented and measurement of duration of reflux in these veins performed.

When cephalad venous flow was induced in the limb under examination, any reflux present was identified on the doppler spectrum. Two typical spectra were selected at each site and the duration of reflux was measured by placing the cursors at the beginning and end of the period of reflux. Time was calculated to the nearest hundredth of a second, to a maximum of 8 seconds, this being limited by the size of the screen (Figure 3.8). Duration of reflux greater than 8 seconds was recorded as 8.00 seconds.

Presence of any turbulent flow was recorded when it led to difficulty in measuring accurately the duration of reflux. The mean of the two readings at each point on the vein was used in subsequent analysis. Where there was a technical difficulty or query over part of the duplex scan, the subject was invited to return to have that part of the scan performed by a radiologist with an Ultramark 9 high-definition imaging colour-flow duplex scanner (Advanced Technology laboratories, Bothwell, Washington) standing upright on a tilting couch and using manual compression for augmentation of venous flow. Where the measurements from these two scans differed significantly, the results of the second scan were used in the analysis. (The difference was considered to be significant if the two results varied by more than 0.29 seconds for a segment where the reflux was less than 1.5 seconds duration. Where the duration of reflux was greater than 1.5 seconds in both scans, significant reflux was considered to be present and the original figures were not altered.) Periodically during the study, as a method of quality control, sequential duplex scans were performed by all three research team members on the same volunteers to allow comparison of results between observers and identification and discussion of any problems.

3.4.6 Other measurements

In addition to the above measurements, each subject had a sample of venous blood taken for examination of various haematological, biochemical and genetic factors. Following attendance at an appointment, subjects were requested to complete a bowel record form which documented the date and time of three consecutive stools. With information from the general questionnaire, the subject's intestinal transit time was

estimated according to the method described by Probert et al. (1993). However, discussion of these results is beyond the scope of this thesis.

3.5 ASSESSMENT OF REPRESENTATIVENESS OF STUDY SAMPLE

3.5.1 Definitions and methods

In this thesis, the term 'non-responders' will be used to describe those subjects who initially agreed to participate in the study and subsequently withdrew or failed to attend their appointment ('withdrawals'), and those subjects who declined to participate in the study from the beginning ('refusals'). The term 'non-participants' will be used to include all those who were invited but did not attend for whatever reason (ie. the non-responders plus the 'returns' and 'unreachables'). The subjects participating in the study will be referred to as 'attenders'.

Several methods were used to assess the representativeness of the study attenders. Comparisons of demographic characteristics were made between the study attenders and (a) the population of Edinburgh and (b) those who were invited but did not attend the study (non-participants). Information on the age and sex distributions of these groups was available from (a) the 1991 Census (General Register Office for Scotland 1993a) and (b) the general practitioners' age-sex registers. The methods used to determine social class are described below. In addition, a follow-up study of a sample of non-responders which was started during the Edinburgh Vein Study data collection period (Diamond 1995), was completed at the end of the study.

3.5.2 Social class according to occupation

To compare the Edinburgh Vein Study population with the population of Edinburgh, social class was classified according to occupation. In the Edinburgh Vein Study, subjects were asked for details of the occupation covering the longest period of their life and their current employment situation (employed/self-employed, unemployed, housewife, retired or student/on a full-time training course) (Appendix 3). Social class was assigned according to the occupation covering the longest period of the subject's life, using the Standard Occupational Classification (Office of Population Censuses and Surveys 1991).

To be comparable with the 1991 Census definitions of 'economically active persons' figures (Office of Populations Censuses and Surveys 1992), the following groups from the Edinburgh Vein Study population were regarded as 'economically inactive' and excluded from the figures for social class:- retired subjects, housewives and students (current and those who were in these groups for the longest period of their lives). Those in the armed forces were classified as 'economically active' but not assigned a social class. Also excluded from the social class figures were those who were currently unemployed and who a) in their Edinburgh Vein Study questionnaire gave no previous job details or who b) in the Census stated that they had no job during the previous ten years (General Register Office for Scotland 1993b).

However two discrepancies between the groups remained. In the Census, students were assigned a social class if they had had a job during the past ten years (Office of Populations Censuses and Surveys 1992). In the Edinburgh Vein Study, no students

were assigned a social class. Finally, there was a separate classification in the Census for those 'on a government scheme'. They were regarded as 'economically active' but were not assigned a social class, and were therefore excluded from the social class figures but they were included in the total figures for 'economic activity' (Office of Populations Censuses and Surveys 1992). (The numbers on such a scheme were relatively small (1782 out of 267655 people aged 18-64 years in the City of Edinburgh ie. 0.7%) (General Register Office for Scotland 1993a)). There was no such classification in the Edinburgh Vein Study and these people would have been classified in the most appropriate available category.

3.5.3 Carstairs deprivation scores

No information was available on the occupation of those who were invited but did not participate in the Edinburgh Vein Study. In order to compare the social status of the non-participants with the study attenders, the Carstairs score for deprivation was used (Carstairs and Morris 1991). This score is based on the subject's postcode sector as illustrated below:-

EH	8	9	AG
area	district	sector	unit

The population in a post-code sector ranges from small numbers to 20000 and averages around 5000 (Carstairs and Morris 1991). Postcodes were available for the majority of subjects in the Edinburgh Vein Study population.

The Carstairs deprivation score ('depscore') is a summary measure applied to populations rather than individuals within a small area, and allows quantification of relative deprivation or affluence in different localities (McLoone 1994). The scores are calculated from the following four variables:-

Overcrowding persons in private households living at a density of more than one person per room, as a proportion of all persons in private households.

Male unemployment proportion of economically active males who are seeking work.

Low social class proportion of all persons in private households with head of household in social class 4 or 5.

No car proportion of all persons in private households with no car.

The original Carstairs scores were based on 1981 Census figures. In the Edinburgh Vein Study, Carstairs scores derived from 1991 Census figures for complete postcode sectors were used, as calculated by McLoone (1994). The four variables listed above were derived from the Small Area Statistics Tables of the 1991 Census. Each variable was standardised and had an equal influence on the resultant score. The four resultant standardised variables were added together to obtain the 'depscore' for each postcode sector (Carstairs and Morris 1991). The original Carstairs scores covered 1010 postcode sectors, had a mean of zero and a standard deviation of 3.61, and ranged from -8.48 (most affluent) to +12.82 (most deprived). The 1991 Carstairs scores were based on 1001 postcode sectors. As in 1981, the all-Scotland mean 'depscore' for 1991 was equal to zero, but the standard deviation was slightly lower at 3.51 (McLoone 1994).

The distribution of 'depscores' has been restructured into a categorical variable called 'depcat', ranging from 'depcat' 1 (most affluent postcode sectors) to 'depcat' 7 (most deprived) (McLoone 1994). The division of the 'depscores' was performed on an arbitrary basis into 7 categories which contained 'populations roughly within plus or minus 0.3, 0.8 and ≥ 1.5 standard deviations of the mean' with 25% of the population in the middle range of -1 to +1 (Carstairs and Morris 1991). Both 'depscores' and 'depcats' are used in the comparison of relative deprivation of attenders and non-participants in the Edinburgh Vein Study.

3.5.4 Follow-up of non-responders

Two methods were used to try to estimate the prevalence of varicose veins in the non-responders.

Survey of non-responders

A survey was carried out of a proportion of the non-responders. For four of the 12 participating practices (practices 1-4), subjects who either refused to participate in the study, or who initially agreed to attend but then subsequently withdrew, were identified. A one page questionnaire was sent to these subjects to inquire about venous disease (Appendix 10). Subjects were asked whether they had ever been diagnosed by a doctor as having varicose veins, leg ulcer or phlebitis and whether they themselves thought they had varicose veins. A further question inquired about any previous treatment for varicose veins.

Information on doctor diagnosed varicose veins from this survey was used to estimate the prevalence of varicose veins in the non-responders. Information on age, sex and Carstairs 'depscore' was used to assess how representative the non-responders who replied to this survey were of all non-responders in practices 1-4. Characteristics of subjects from practices 1-4 were compared with those from the remaining practices in the Edinburgh Vein Study, to assess the representativeness of these four practices of the whole study population.

Telephone reporting

Attempts were made to reach by telephone subjects who did not respond to the initial letters of invitation to the Edinburgh Vein Study. Subjects contacted by telephone in this way, who declined the invitation to participate in the study during the telephone conversation, were asked if they themselves thought that they had varicose veins. Additional information was obtained in this way on self-reported varicose veins from a proportion of non-responders from all practices of the Edinburgh Vein Study.

3.6 ANALYSIS OF RESULTS

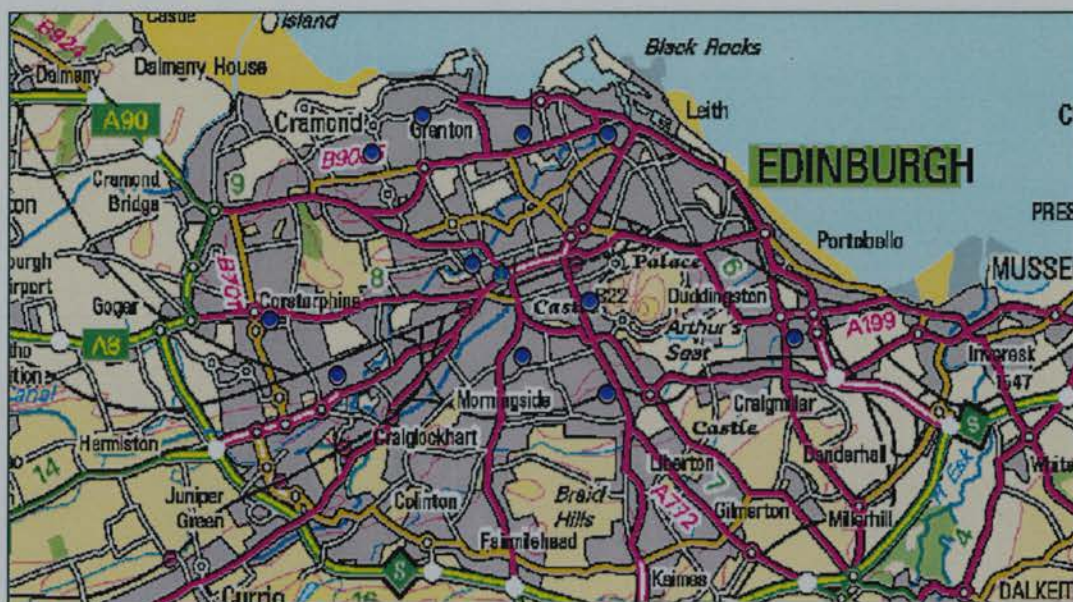
Information from the recording forms and questionnaires was entered onto a DBASE IV database by the research secretary or clinical research fellow. Prior to analysis, all the examination and questionnaire data were entered by a second person. Comparison of the two databases was performed to identify discrepancies which were checked and corrected. The data files were transferred to the Edinburgh University Mainframe computer for analysis using the SPSS-X and SAS statistical packages.

The following statistical tests were used:- chi-squared test (or Fisher's exact test where the cell frequencies were small) and Mantel-Haenszel test for linear association for categorical data, Student's t-test for continuous parametric data, the Mann-Whitney test for continuous non-parametric data and the Kappa statistic as a measure of agreement between categorical variables (Fleiss 1981). The age-adjusted prevalence rates were calculated using GLIMMIX (a SAS macro) which fits generalised linear mixed models. Duplex scanning results were compared using cut-off points for reflux duration of ≥ 0.5 seconds ($RD \geq 0.5$) and > 1.0 second ($RD > 1.0$) to define reflux.

3.7 SUMMARY

The Edinburgh Vein Study was a cross-sectional survey of men and women aged 18-64 years, randomly selected from the age-sex registers of 12 General Practices in Edinburgh. Subjects completed a self-administered questionnaire enquiring about demographic details, past medical and family history, dietary habits and lifestyle factors. They underwent a clinical examination of their legs and had colour photographs taken to document any signs of venous disease. A duplex scan of points on the deep and superficial veins was performed to detect the presence of any venous reflux. To enable the representativeness of the study population to be assessed, certain demographic characteristics of the attenders were compared to (a) the population of the city of Edinburgh and (b) the non-participants in the study. Finally, a follow-up study was conducted to assess the prevalence of venous disease in a sample of the non-responders.

Figure 3.1 General Practices participating in the Edinburgh Vein Study



Footnote:

- Participating practices represented by blue circles
- 11 practice locations shown (2 practices shared the same premises)

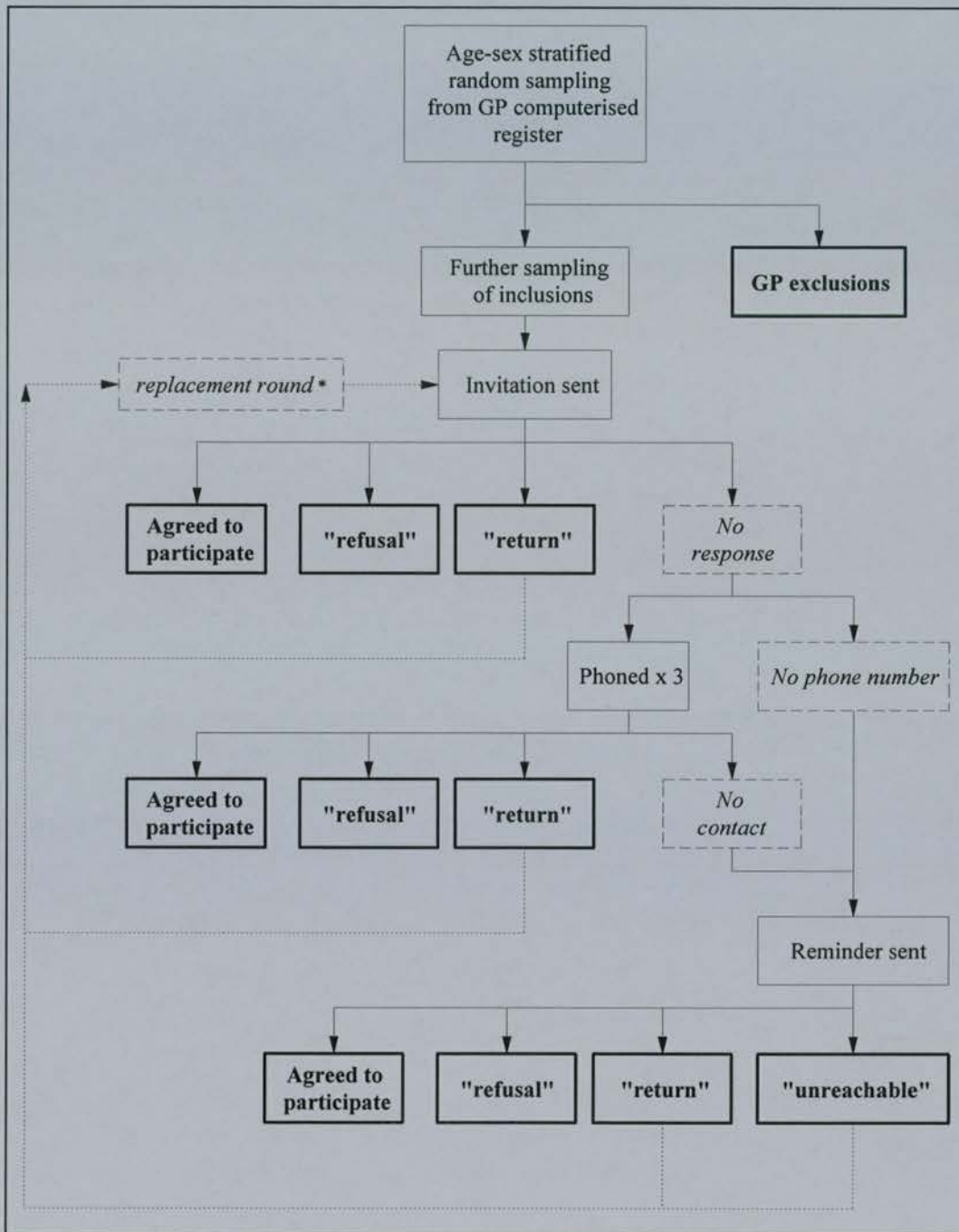
Table 3.1 Number of subjects selected from each general practice participating in the Edinburgh Vein Study

Practice	1 & 2	3-11	12
Number selected from age-sex register	300	450	600
Number invited in first round from all 10 year age bands	160	240	368
Number invited in first round from 7 year age band	28	42	64
Total per practice invited in first round	188	282	^a 432

Footnote:

- ^aNo second round of invitations was performed for Practice 12

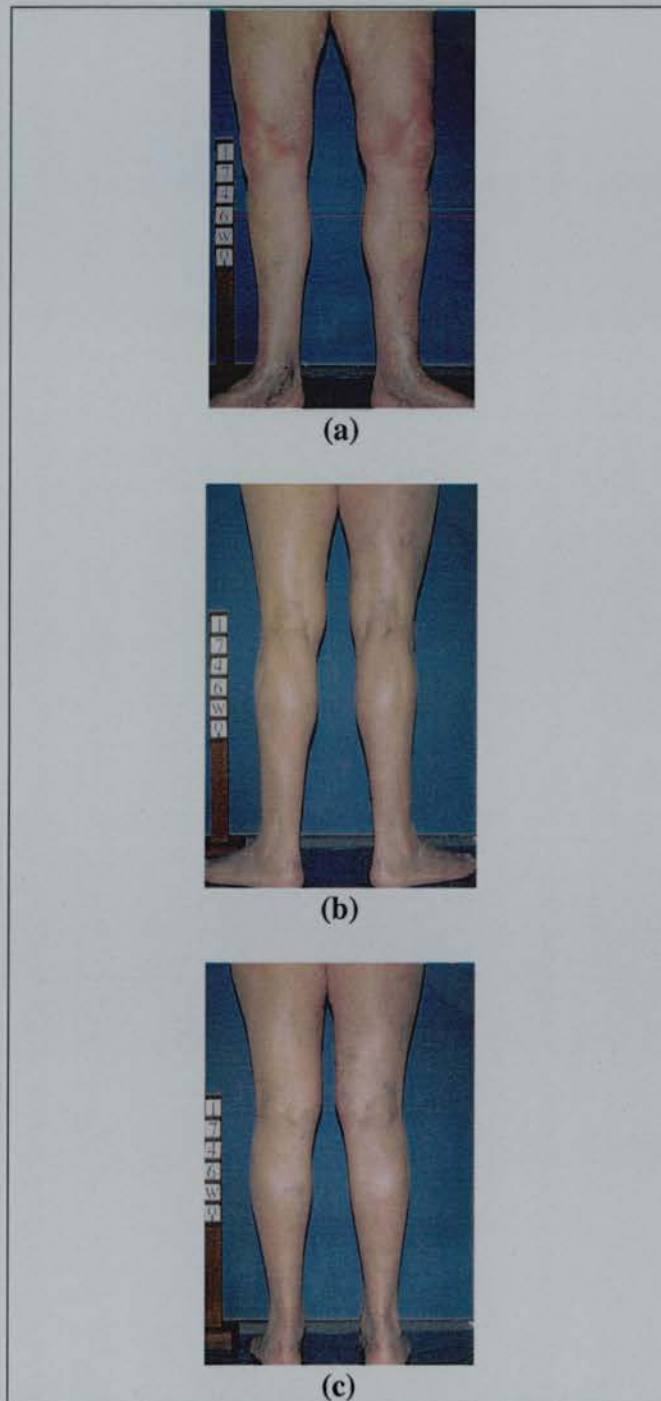
Figure 3.2 Recruitment cycle for the Edinburgh Vein Study



Footnote:

- *one round of replacement invitations for Practices 1-11 only
- 'returns' = subjects who had moved out of the area or whose letters were returned by the post office or subsequent occupier
- 'unreachables' = subjects with whom no contact was made, despite two invitations and telephone calls where possible

Figure 3.3 Three standard positions for examination of subjects
in the Edinburgh Vein Study



Footnote:

- (a) Facing towards the examiner with heels together and forefeet spread apart
- (b) Facing away from the examiner with heels together and forefeet spread apart
- (c) Facing away from the examiner with feet parallel

Figure 3.4 Trunk varices in silhouette on the left lower leg



Figure 3.5 Hyphenweb and reticular varices



Footnote:

- Hyphenweb varices on the thigh
- Reticular varices around the knee

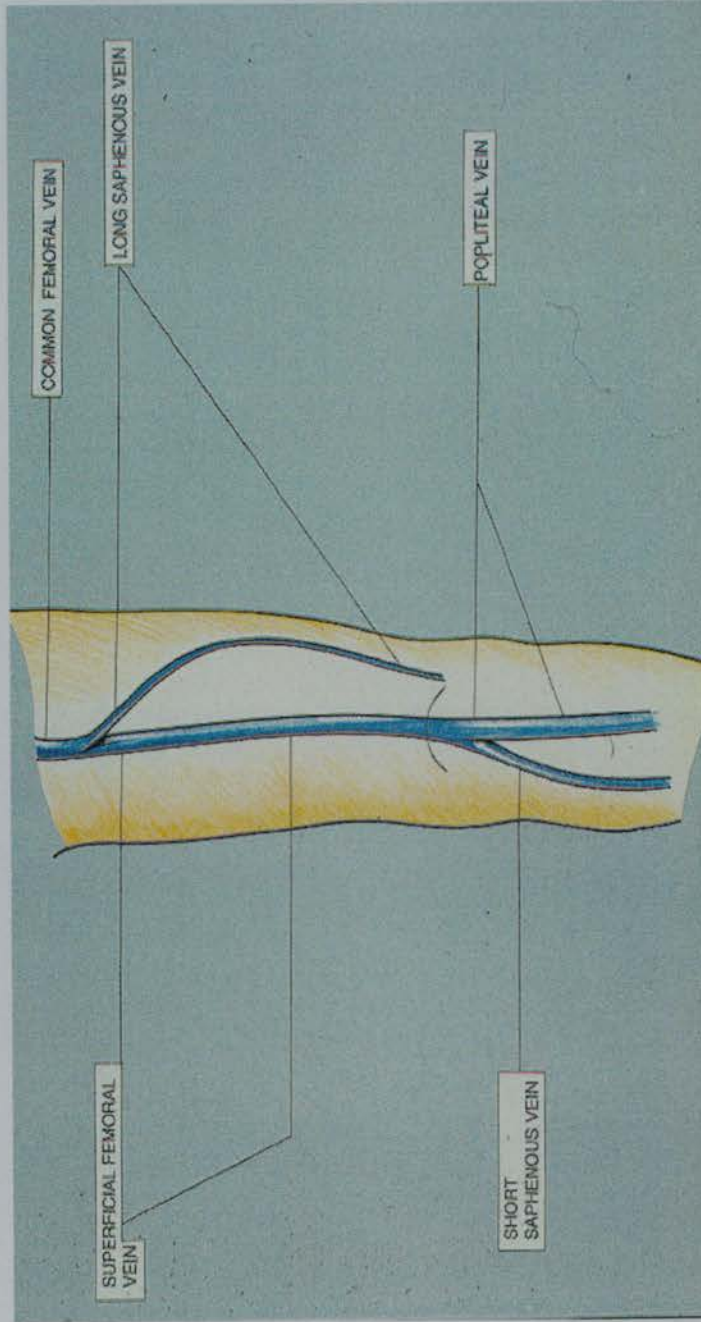
Figure 3.6 Grade 2 chronic venous insufficiency



Footnote:

- Pigmentation on lower leg with venous flare at the ankle

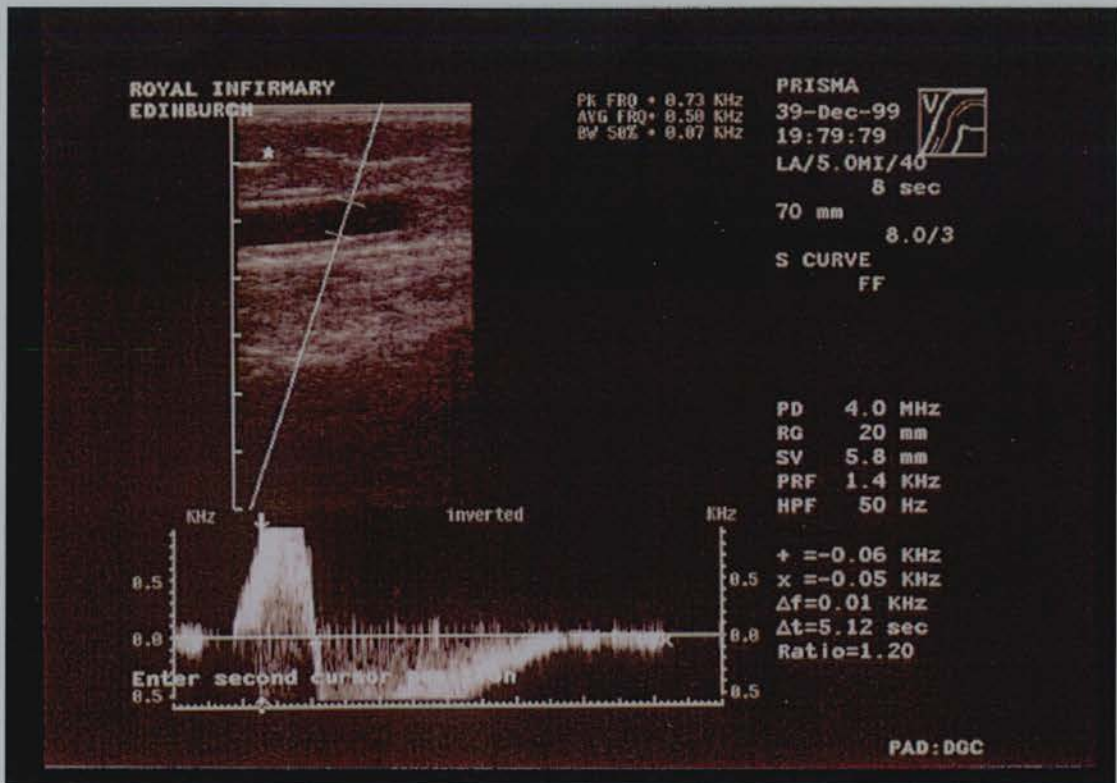
Figure 3.7 Sites on the leg veins assessed by duplex scanning in the Edinburgh Vein Study



Footnote:

- Common femoral vein
 - Superficial femoral vein
 - Popliteal vein
 - Long saphenous vein
 - Short saphenous vein
- proximal to the sapheno-femoral junction
 (i) approximately 2cm distal to the confluence with the profunda femoris vein
 (ii) in the lower third of the thigh
 (i) above and (ii) below the knee crease
 (i) just distal to the sapheno-femoral junction
 (ii) in the lower third of the thigh
 just distal to the sapheno-popliteal junction

Figure 3.8 Measurement of reflux in the long saphenous vein by duplex scanning



Footnote:

- Reverse flow is represented in the spectrum in the lower half of the picture by shading under the horizontal line. In this example, duration of reflux is 5.12 seconds.

CHAPTER 4

RESULTS I

RESPONSE RATES AND CHARACTERISTICS

OF THE STUDY POPULATION

4.1 INTRODUCTION

In any study, it is important to know whether the final study sample is representative of the target population from which it was selected. If non-participants differ significantly from study participants with regard to a factor under investigation, the results of the study will reflect a distorted picture of that factor within the target population. However, it is often difficult to determine the representativeness of the study sample due to a lack of information on the factor of interest for the whole study population. In such cases, a comparison may be made of known characteristics of study participants and non-participants, such as age, sex and social class. Significant differences between the groups regarding these variables may lead the investigators to doubt the representativeness of their sample. Further follow-up of the non-responders is then required to enable the extent of the non-response bias to be estimated.

This chapter presents details of the response in the Edinburgh Vein Study. The demographic characteristics of the study attenders are compared with those of subjects

who were invited but did not attend the study, and with those of the wider Edinburgh population. Results of further follow-up of the non-responders are presented in Chapter 5.

4.2 RESPONSE RATES

In the Edinburgh Vein Study, 5250 names were extracted from the computerised age-sex registers of the 12 participating general practices. The General Practitioners excluded 343 names because they were either considered unsuitable to be approached or because they had moved away from the practice. A total of 4101 invitations were sent in the first and second round of invitations. An additional two subjects have been included, bringing the total number invited to 4103. These were two fathers who responded to the invitation letter intended for their sons of the same name at the same address, and who had been examined in the study before the error became apparent.

Of the 4103 subjects invited, a total of 618 subjects had either moved out of the area, had their letters returned by the General Post Office or other occupiers, or when their telephone number was contacted, were not living at that number and had no other point of contact ('returns'). Of the remaining 3485 subjects, no contact at all was made with 573 ('unreachables') and a further 998 indicated that they did not wish to take part in the study ('refusals'). The remaining 1914 subjects agreed to participate but of these, 348 subsequently did not attend or withdrew prior to their appointment ('withdrawals'). This resulted in a final study population of 1566 subjects ('attenders').

The response rates in the Edinburgh Vein Study by sex are shown in Table 4.1. A total of 1566 attenders out of 4103 subjects invited resulted in a crude response rate of 38.2%. Excluding the 'returns' (who were effectively ineligible to participate in the study) from the denominator gave an adjusted response rate of 44.9%. Assuming that none of the 'unreachables' received their invitation letter and excluding them from the denominator resulted in a final response rate of 53.8% of eligible people contacted. It is this final response rate which will be used in the following discussion.

4.3 AGE AND SEX

The proportions of attenders and non-participants in each age band are shown in Table 4.2. Of the initial invitations, 14.9% were sent to the youngest age band which spanned 7 years, and 21.3% in each of the four remaining ten year age bands. However, different numbers of replacement invitations for 'returns' and 'unreachables' resulted in variations in the final total invited in each age band.

Of the study attenders 16.7% were in the 25-34 year ageband compared with 26.9% in the 55-64 year ageband (Table 4.2). While the proportion of non-responders in each age band was similar, 62.1% of the 'returns' and 53.6% of the 'unreachables' were between 18 and 34 years old. In addition, more of those not contacted were male than female (64.9% of the 'returns' and 56.2% of the 'unreachables'). Compared to the non-responders, the attenders were significantly older and contained a higher proportion of females (55.4% versus 48.8%) (both $p \leq 0.001$). Similarly, the attenders were

significantly older and contained a higher proportion of females (55.4% versus 44.3%) than all the 'non-participants' combined (both $p \leq 0.001$).

Table 4.3 shows the final response rate in the Edinburgh Vein Study by age and sex. The response rate was 56.9% for females and 50.4% for males, and increased with age from 34.3% in the 18-24 year olds to 61.3% in the 55-64 year olds. Of the study attenders, 867 (55.4%) were female and 699 (44.6%) were male. There was no significant difference between the mean age of the females and the males who participated (44.78 years versus 45.85 years, $p > 0.05$).

Figure 4.1 compares the age distribution of the Edinburgh Vein Study attenders with the population of the City of Edinburgh aged 18-64 years, according to the 1991 census figures (General Register Office for Scotland 1993a). The Edinburgh Vein Study population contained proportionally more older people (45-64 years) and fewer younger people (18-34 years) than the population of the City of Edinburgh as a whole. Of the study population, 16.7% were in the 25-34 year age group and 26.9% in the 55-64 year age group, compared with 27.2% and 16.7% respectively in the City of Edinburgh population. Females accounted for 55.4% of the Edinburgh Vein Study population, compared with 51.6% of the City of Edinburgh population aged 18-64 years.

4.4 ETHNIC ORIGIN

Of the 1566 study attenders, 1548 (98.9%) were White Caucasian, seven (0.4%) were Chinese and three (0.2%) each were African and Indian. Of the five (0.3%) in the

'other' group, three were Iranian, one was Korean and one was Central American/White Caucasian. The 1991 Census figures showed that 97.7% of the City of Edinburgh population in the 18-64 year age group were White Caucasian. The ethnic minorities with the highest representations were Pakistanis comprising 0.6% of this age group and Chinese accounting for 0.5% (General Register Office for Scotland 1993a).

4.5 SOCIAL CLASS

Two analyses of social class and response were made:- between the study attenders and the City of Edinburgh population and between the study attenders and non-responders.

4.5.1 Comparison of study attenders with the City of Edinburgh population

Figure 4.2 compares the social class distribution of the 'economically active' people in the Edinburgh Vein Study population compared to the figures for the 10% sample of the City of Edinburgh population aged 16 years and over, obtained from the 1991 Census (General Register Office for Scotland 1993c). Similar patterns exist between the two population samples. The majority of people were in social classes II or III in both the Edinburgh Vein Study population (37.0% and 24.8%) and the City of Edinburgh population (30.4% and 26.3%). Both populations followed the same decreasing trend from social class II through to social class V. The Edinburgh Vein Study population had slightly lower proportions in social classes IV and V than the City

of Edinburgh population (7.1% and 4.4% versus 11.3% and 6.3% respectively) and a higher proportion in social class I (10.8% versus 8.5%).

To be comparable with the Edinburgh Vein Study classification, the 'economically active' students from the 1991 Census were classified as 'economically inactive' (General Register Office for Scotland 1993a, Office of Population Censuses and Surveys 1992) (see Section 3.5.2). After the above reclassification, 76.9% of the City of Edinburgh population aged 18-64 years were 'economically active' compared to 78.0% of the Edinburgh Vein Study population.

4.5.2 Comparison of study attenders with non-participants

Of the 4103 subjects invited to participate in the Edinburgh Vein Study, postcodes were missing for 259 of them, including 118 attenders. Of the 259 missing postcodes, 197 were from Practice 10. This practice had a different computerised method of recording the postcodes and only the area and district of the postcode were made available, which was insufficient for calculating the 'depscore' (see Section 3.5.3). However since similar proportions of postcodes were missing for the attenders (62.5%) and all the non-participants (60.5%) in this practice, it was decided not to exclude the practice from the analysis of deprivation. Furthermore, Practice 10 was on the same premises and serving the same population as Practice 4, which had only 2 missing postcodes. Practice 4 had a higher proportion of invited subjects in the more affluent 'depcats' when compared to all the invited subjects from Practices 1-12 (89.9% in 'depcats' 1-3 compared with 47.5% in the total population invited). From the 'depcats' available, it

would seem that Practice 10 was following a similar pattern to its sister Practice 4 (84.7% of the invited subjects in 'depcats' 1-3 in Practice 10). Given this assumption, the effect of the missing postcodes from Practice 10 would be a slight reduction in the true proportion of the study population in the more affluent categories.

Table 4.4 shows the 'depcats' of the attenders and the different groups of non-participants in the Edinburgh Vein Study. The attenders had a larger proportion of their subjects in the more affluent 'depcats' 1-3 (56.1%) compared with the total group invited to participate (47.5%), and a correspondingly smaller proportion in the more deprived 'depcats' 4-7. Conversely, the 'unreachables' had a smaller proportion of its subjects in the more affluent 'depcats' 1-3 (27.1%) and a correspondingly larger proportion in the more deprived 'depcats'. The non-responders and the 'returns' had a similar proportion of subjects in each 'depcat' when compared to the total group invited to participate.

The 'depscores' for the total group invited were skewed towards the more affluent categories. The median 'depscore' (50th percentile) and the 25th and 75th percentile for each group of attenders and non-participants are shown in Table 4.5. The median 'depscore' of the attenders was significantly lower (more affluent) than that of the non-responders, and of all the non-participants combined (both $p \leq 0.001$). The 'unreachables' had a significantly higher (more deprived) median 'depscore' than that of the other subjects invited ($p \leq 0.001$).

4.6 SUMMARY

In summary, more females than males and more older than younger people attended the Edinburgh Vein Study. Of the people invited to participate, those in the younger age-groups, particularly the males, were more difficult to contact and were more likely to have moved address. The resulting study population contained a higher proportion of older people and a slightly higher proportion of females when compared with the population of the City of Edinburgh in a similar age range.

The attenders at the Edinburgh Vein Study came from relatively more affluent areas than (a) the non-responders and (b) all the non-participants combined. The 'unreachables', who were unable to be contacted at all, came from relatively more deprived areas. When assessed according to occupation, the overall social class distribution of the study population followed a similar pattern to the general population of Edinburgh aged 16 years and over, although a higher proportion of the study attenders were in social classes I and II.

Table 4.1 Number of attenders and non-participants and response rates in the Edinburgh Vein Study by sex

	Attenders (n) [a]	Invited (n) [b]	Returns (n) [c]	Unreachables (n) [d]	Crude Response (%) [a/b] x 100	Adjusted Response (%) [a/(b-c)] x 100	Final Response (%) [a/(b-(c+d))] x 100
Females	867	1992	217	251	43.5	48.8	56.9
Males	699	2111	401	322	33.1	40.9	50.4
Total	1566	4103	618	573	38.2	44.9	53.8

Footnote:

- Columns [a] – [d] show numbers of subjects (n)

Table 4.2 Attenders and non-participants in the Edinburgh Vein Study by age band

Age (years)	18-24		25-34		35-44		45-54		55-64		Total	
	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)
Attenders	8.4	(131)	16.7	(261)	22.0	(344)	26.1	(408)	26.9	(422)	26.9	(422)
Non-responders	18.6	(251)	21.4	(288)	20.7	(279)	19.5	(262)	19.8	(266)	19.8	(266)
Returns	26.5	(164)	35.6	(220)	19.6	(121)	10.2	(63)	8.1	(50)	8.1	(50)
Unreachables	25.3	(145)	28.3	(162)	20.9	(120)	15.9	(91)	9.6	(55)	9.6	(55)
Total invited	16.8	(691)	22.7	(931)	21.1	(864)	20.1	(824)	19.3	(793)	19.3	(793)

Footnote:

- % = proportion in each age band within individual subject groups
- n = number of subjects within each group

Table 4.3 Final response rate in the Edinburgh Vein Study by age and sex

Age (years)	18-24		25-34		35-44		45-54		55-64		Total	
	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)
Males	30.2	(55)	41.4	(103)	55.1	(158)	55.4	(181)	58.9	(202)	50.4	(699)
Females	38.0	(76)	52.7	(158)	55.4	(186)	66.2	(227)	63.8	(220)	56.9	(867)
Total	34.3	(131)	47.5	(261)	55.2	(344)	60.9	(408)	61.3	(422)	53.8	(1566)

Figure 4.1 Age distribution of Edinburgh Vein Study population and City of Edinburgh population aged 18-64 years

(General Register Office for Scotland 1993a)

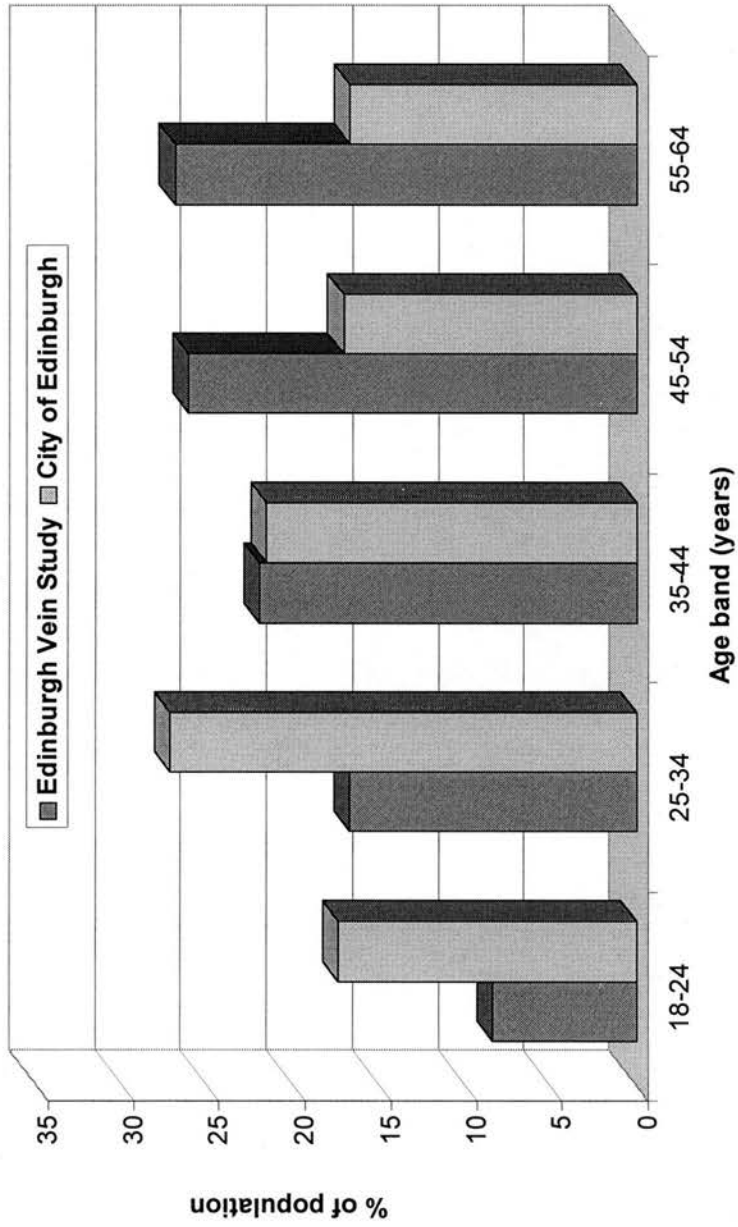


Figure 4.2 Social class of 'economically active' persons in the Edinburgh Vein Study and City of Edinburgh population (10% sample aged 16 years and over)

(General Register Office for Scotland 1993c)

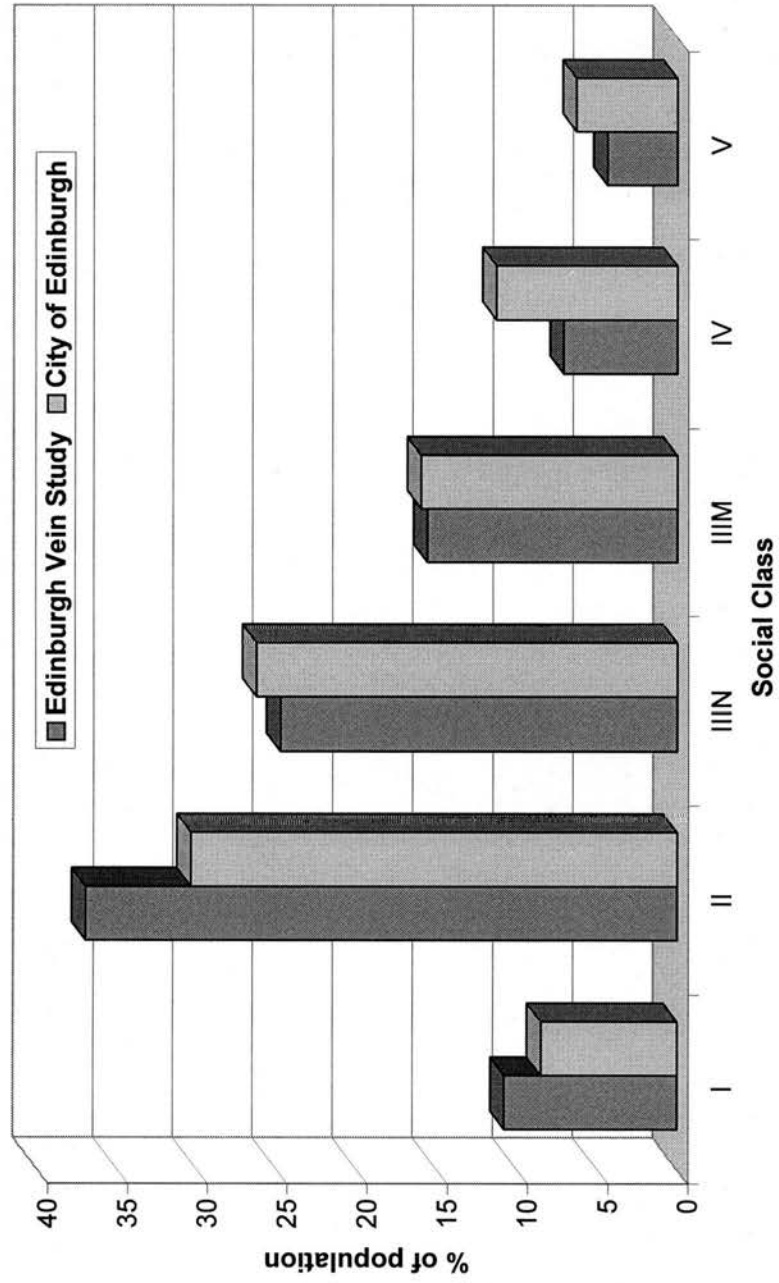


Table 4.4 Proportion of attenders and non-participants in the Edinburgh Vein Study in each

Deprivation Category ('depcat' 1-7) (Carstairs and Morris 1991)

	Proportion (%) in Depcat						
	1	2	3	4	5	6	7
(n)							
Attenders	15.7	12.9	27.5	16.7	15.7	4.1	7.3
Non-responders	10.4	10.6	25.0	18.4	16.2	5.2	14.2
Returns	10.9	12.3	25.6	16.7	18.1	4.4	12.1
Unreachables	4.1	5.6	17.4	17.8	22.1	5.7	27.3
Total invited	11.6	11.0	24.9	17.4	17.2	4.7	13.2

Footnote:

- Missing values due to missing postcodes: Attenders = 118; Non-responders = 94; Returns = 31; Unreachables = 16

Table 4.5 Deprivation scores ('depscore') of attenders and non-participants in the Edinburgh Vein Study (Carstairs and Morris 1991)

		Depscore		
	(n)	25 th percentile	50 th percentile	75 th percentile
Attenders	1448	-3.66	-1.34	+1.14
Non-responders	1252	-2.81	-0.34	+1.89
Returns	587	-3.00	-0.89	+2.21
Unreachables	557	-1.25	+1.18	+6.55
Total invited	3844	-3.00	-0.51	+1.89

Footnote:

- Missing postcodes: Attenders n = 118; Non-responders n = 94; Returns n = 31; Unreachables n = 16

CHAPTER 5

RESULTS II

PREVALENCE OF VENOUS DISEASE

5.1 INTRODUCTION

In the Edinburgh Vein Study, several methods of measurement were used to assess the presence of venous disease. Subjects had their legs examined for signs of varicose veins and CVI. In addition, photographs of the legs were independently analysed for signs of venous disease. Finally, duplex scanning of the deep and superficial veins of the legs was performed to detect the presence of venous reflux. The results of duplex scanning are presented in Chapter 6. This chapter describes the prevalence of clinical signs of venous disease, based on the examination findings. In addition, a comparison with results based on the photographic slide analysis is reported. Finally, the analysis of results from the survey of non-responders is presented, including an estimate of the prevalence of varicose veins in this group of non-participants. An attempt is made to quantify the effect that non-response bias may have had on the prevalence of varicose veins detected in the Edinburgh Vein Study, and an estimate of the true prevalence of varicose veins in the target population is proposed.

5.2 PREVALENCE OF VENOUS DISEASE

The following results are based on the findings from clinical examination of subjects in the Edinburgh Vein Study.

5.2.1 Prevalence by sex

The age-adjusted prevalence of trunk varices (grades 1-3) was 39.7% in men and 32.2% in women ($p \leq 0.01$). Table 5.1 shows that the majority of affected subjects had mild (grade 1) trunks and the difference between the sexes reached statistical significance for grade 1 only ($p \leq 0.01$). Hyphenweb and reticular varices were very common, each affecting over 80% of subjects, although the majority had these varices only to a mild degree (grade 1). Among the smaller numbers affected by grade 2 hyphenweb and reticular varices, women had a significantly higher prevalence than men (both $p \leq 0.05$). The age-adjusted prevalence of CVI (grades 1-3) was 9.4% in men and 6.6% in women ($p \leq 0.05$). However, sex differences were not statistically significant when the grades of severity were analysed individually ($p > 0.05$). A total of 10 subjects (8 men and 2 women) had current or previous venous ulceration (grade 3 CVI). The age-adjusted prevalence of 'perforators' was 14.6% in men and 3.0% in women ($p \leq 0.001$). The age-adjusted prevalence of pitting ankle oedema was 7.4% in men and 16.0% in women ($p \leq 0.001$).

There were 17 women and 3 men who reported having had an operation for varicose veins in their questionnaire, but in whom no trunk varices were found on examination. If it was assumed that all of these subjects had trunk varices prior to

their operations, then the resulting age-adjusted prevalence of trunk varices increased to 40.1% in men and 34.2% in women ($p \leq 0.05$).

5.2.2 Prevalence by side of the body

Table 5.2 shows the prevalence of varicose veins and CVI in the right and left legs separately. There was no significant difference in the prevalence between the two sides, in any grade of any of the four disease categories (all $p > 0.05$).

5.2.3 Prevalence by age

The prevalence of trunk varices by age is shown in Table 5.3. The prevalence increased linearly with age in both sexes, and ranged from 11.5% in the 18-24 year olds to 55.7% in the 55-64 year olds when both sexes were combined ($p \leq 0.001$). Likewise, the prevalence of both reticular and hyphenweb varices increased with increasing age in both sexes (all $p \leq 0.001$) (data not shown). Figure 5.1 shows that, under the age of 35 years, CVI was extremely rare in women and did not occur at all in men. Overall, the prevalence of CVI increased markedly with age ($p \leq 0.001$). In the oldest age group of 55-64 years, the prevalence of CVI was much higher in men (25.2%) than women (12.3%) ($p \leq 0.001$). However, even in this age group, most of those affected had only mild (grade 1) CVI (18.3% of men and 8.6% of women). The prevalence of 'perforators' and pitting ankle oedema increased with increasing age (both $p \leq 0.001$).

5.2.4 Prevalence by social class and deprivation

There was no obvious relationship between social class (classified by occupation) and the age- and sex-adjusted prevalence of either trunk varices or CVI (Table 5.4). The age- and sex-adjusted prevalence of both conditions was higher in manual workers (social classes IIIM-V) than non-manual workers (social classes I-IIIN) but these differences were not statistically significant (both $p>0.05$). When the study attenders were analysed according to the presence or absence of trunk varices, there was no significant difference in the median deprivation scores of the two groups ($p>0.05$).

5.2.5 Prevalence by body mass index

The median body mass index (BMI) was 25.4 kg/m² in men (inter-quartile range 23.2 to 27.8), and 24.5 kg/m² in women (inter-quartile range 22.1 to 27.6). In both men and women there was an increase in age across sex-specific BMI quartiles, ranging from 38.9 years to 49.9 years in women, and from 41.0 years to 49.8 years in men, in the lowest and highest BMI quartiles respectively. In women, there was an apparent increase in the prevalence of trunk varices across increasing quartiles of BMI but this trend disappeared when prevalences were adjusted for age ($p>0.05$) (Figure 5.2a). In men, the age-adjusted prevalence of trunk varices decreased linearly across increasing BMI quartiles ($p\leq 0.001$) (Figure 5.2a). For CVI, the lowest BMI quartile had the highest age-adjusted prevalence in men and the lowest age-adjusted prevalence in women. However, there was no significant linear trend in

the age-adjusted prevalence of CVI across BMI quartiles for either sex (both $p>0.05$) (Figure 5.2b).

5.3 PREVALENCE OF PREVIOUS VARICOSE VEIN TREATMENT

In the main study questionnaire, subjects were asked if they had ever had treatment for varicose veins. The reported prevalence of different forms of treatment, adjusted for age, were as follows:- compression treatment (stockings or bandaging) 2.9% in men and 9.0% in women ($p\leq 0.001$); operations 5.1% in men and 7.8% in women ($p\leq 0.05$); injections 1.4% in men and 5.7% in women ($p\leq 0.001$).

5.4 ASSESSMENT OF STUDY METHODS

5.4.1 Comparison of methods of measurement

A classification of venous status based on analysis of photographic slides was available for 1555 of the 1566 subjects in the study. This slide-based classification of venous status was compared with the classification from examination of the subject in the clinic. Measures of agreement for the two methods were obtained for (i) individual subjects, taking the leg with the higher grade as the subject's score, and (ii) individual legs. Comparison of classification into 'disease present/absent' is shown in Table 5.5(a). There was generally 'fair to good' agreement (Fleiss 1981) for all categories of disease although agreement was clearly better for trunks and CVI than for hyphenwebs and reticular varices.

Table 5.5(b) shows comparison of methods for classifying grades of disease. Overall there was 'fair to good agreement' between the two classification methods for trunk varices and CVI, but 'poor agreement' for hyphenwebs and reticular varices. Further analysis showed that trunk and hyphenweb varices were more likely to be classified at a higher grade by the examination method, while reticular varices were more likely to be classified at a higher grade from the slide analysis (data not shown).

5.4.2 Comparison of observers' results

Observer 3 mainly examined subjects at the evening clinics, and as a result saw a younger population (mean age 43.0 years) with a higher proportion of males (47.5%) compared to those examined by Observer 1 (mean age 45.5 years, 43.3% males) and Observer 2 (mean age 45.7 years, 45.0% males). The comparison of observers' classifications is therefore limited to the populations examined by the two principal observers (Observers 1 and 2).

The age-adjusted prevalence of varices and CVI reported by the two principal observers were compared. Observer 1 classified 35.9% of subjects as having trunk varices and 8.2% as having CVI, compared with 36.7% and 8.0% respectively for Observer 2 (both $p>0.05$). Similarly there were no significant differences in the prevalence of hyphenweb or reticular varices classified by these two observers (both $p>0.05$). The age-adjusted prevalence of the different disease categories classified by the two principal observers according to sex, is shown in Table 5.6. Once again, there were no significant differences between these observers (all $p>0.05$).

5.5 VENOUS STATUS OF NON-RESPONDERS

5.5.1 Survey of non-responders

Results

In practices 1-4 there were 381 non-responders (103 'withdrawals' and 278 'refusals'). A one page questionnaire was sent to 378 of these non-responders inquiring about venous disease and 194 (51.3%) of these questionnaires were returned. For the following results, proportions were based on the number of complete answers to individual questions.

Twenty-six (13.8%) non-responders thought they had varicose veins. When asked if they had been told by a doctor that they had any of the following conditions, 11 (5.8%) had been given a diagnosis of varicose veins, 1 (0.6%) leg ulcer and 5 (2.8%) phlebitis. The 446 attenders from Practices 1-4 were asked the same questions about previous diagnosis in the main study questionnaire. The results were as follows:- 62 (13.9%) had been given a diagnosis of varicose veins, 9 (2.0%) leg ulcer and 15 (3.4%) phlebitis. To allow a meaningful comparison to be made between the attenders and non-responders, the results for diagnosis of varicose veins were adjusted for differences in age and sex between the two groups. After adjustment, 6.5% of the non-responders reported a doctor's diagnosis of varicose veins compared with 13.3% of the attenders ($p \leq 0.05$). In men, there was no significant difference in the age-adjusted prevalence of doctor diagnosed varicose veins between the non-responders and the attenders (6.7% versus 9.1% respectively, $p > 0.05$). However, among the women, the prevalence of doctor diagnosed varices was significantly lower in the non-responders than the attenders

(6.5% versus 16.7% respectively, $p \leq 0.05$). The age-adjusted prevalence data for doctor diagnosed varicose veins was extrapolated to all the non-responders in practices 1-4. The resulting estimates suggested that a higher proportion of women than men with a doctor's diagnosis of varices attended the study (77.4% versus 58.1%), while a similar proportion of women and men without a doctor's diagnosis attended (53.9% versus 50.1%) (Figure 5.3).

Regarding treatment, 5 (2.6%) of the non-responders who returned their questionnaires reported having had an operation for varicose veins, 3 (1.6%) injections and 5 (2.7%) compression treatment. This compared to 28 (6.4%), 20 (4.6%) and 26 (5.9%) respectively of the attenders from Practices 1-4. The number of non-responders reporting previous treatment or doctor diagnosed venous conditions other than varicose veins were too small to allow adjustment for age for comparison with attenders' data.

Characteristics of non-responders who replied to the questionnaires

Of the 378 non-responders in practices 1-4 who were sent questionnaires, 186 (49.2%) were female. There was no significant difference between the proportion of men and women returning their questionnaires (49.5% and 53.2% respectively, $p > 0.05$). Similarly there was no significant difference in age band between these two groups ($p > 0.05$). However those who returned their questionnaires had a significantly lower (more affluent) median Carstairs deprivation score (-2.56, inter-quartile range -3.66 to

+0.81) than those who did not return their questionnaires (-1.34, inter-quartile range -3.00 to +1.14) ($p \leq 0.05$).

Characteristics of Practices 1-4

The survey of non-responders was based on a sample of one third of the participating practices (practices 1-4). In order to assess how representative these practices were of the whole study population, a comparison was made between the characteristics of the study attenders and non-responders from practices 1-4 with those from the remaining practices (practices 5-12).

There was no significant difference between the study attenders from the two groups of practices with regard to age, sex or social class based on occupation (all $p > 0.05$). Likewise, there was no significant difference in the prevalence of trunk varices between the attenders from practices 1-4 and practices 5-12 (38.1% versus 34.6%, $p > 0.05$). However the attenders from practices 1-4 had a significantly lower (more affluent) median Carstairs deprivation score (-2.56, inter-quartile range -3.54 to +0.81) than the attenders from practices 5-12 (-1.25, inter-quartile range -3.79 to +1.22) ($p \leq 0.01$).

Comparison of the non-responders from practices 1-4 with those from practices 5-12 revealed no significant differences in the age band or sex composition of the two groups ($p > 0.05$). However, the non-responders from practices 1-4 had a significantly lower (more affluent) median Carstairs deprivation score (-2.42, inter-quartile range

-3.54 to 1.14) than those from practices 5-12 (+0.35, inter-quartile range -2.74 to +3.10) ($p \leq 0.001$).

5.5.2 Telephone reporting of varicose veins

Of the 998 subjects who declined to participate in the Edinburgh Vein Study, 568 had been contacted personally by telephone to elicit their response to the initial invitation. At the time of contact, subjects were asked if they had varicose veins. In 46 cases the varicose vein status remained unknown, either because the subject did not know themselves, or because the question was not asked or answered. Of the remaining 522 subjects, 57 (10.9%) said that they had varicose veins. When adjusted for age, 3.7% of men and 18.6% of women reported on the telephone that they had varicose veins ($p \leq 0.001$).

5.5.3 Estimate of the prevalence of varicose veins in the total study population

The difference between the prevalence of a doctor's diagnosis of varicose veins reported in the study questionnaire and the prevalence of varices found on examination in the attenders was extrapolated to the non-responders. Using this method, the prevalence of varicose veins which would have been found in the non-responders had they participated in the study was estimated at 21.9% in the men and 11.5% in the women (Table 5.7). If this prevalence was assumed to apply to all the non-responders, then the true prevalence of varicose veins in the eligible population contacted would be reduced to 31.3% in men and 23.0% in women (Figure 5.4).

5.6 SUMMARY

Approximately one third of the study population had trunk varicose veins and more than 80% had reticular and hyphenweb varices. Mild trunk varices and CVI were more common in men than women, but the prevalence of previous treatment was more common in women. The prevalence of all categories of disease increased with age. There was no significant association between trunk varices or CVI and social class. There was no consistent relationship between trunk varices or CVI and BMI, although there was a decreasing trend for trunk varices across increasing BMI quartiles in men. A survey of a sample of the non-responders suggested that the prevalence of previously diagnosed varicose veins was significantly lower in female non-responders compared to female attenders. Extrapolation of results from this survey suggested that a higher proportion of affected women than affected men attended the study. Taking estimates of the non-response bias into account, the 'true' prevalence of varicose veins in the target population was proposed at 31% for men and 23% for women.

Table 5.1 Age-adjusted prevalence of varicose veins and chronic venous insufficiency (CVI) by sex

	Grade	Males		Females		p value
		%	(n)	%	(n)	
Trunks	1	33.3	(238)	26.2	(223)	**
	2	5.4	(39)	5.6	(47)	NS
	3	1.0	(7)	0.5	(4)	NS
Hyphenwebs	1	79.2	(554)	84.4	(732)	NS
	2	5.9	(44)	9.2	(76)	*
	3	0	(0)	0.6	(5)	-
Reticulars	1	81.6	(571)	85.3	(739)	NS
	2	4.0	(29)	6.4	(54)	*
	3	0	(0)	0	(0)	-
CVI	1	6.9	(51)	5.3	(44)	NS
	2	1.3	(10)	1.1	(9)	NS
	3	1.0	(8)	0.2	(2)	NS

Footnote:

- (n) = number in each group with varices /CVI
- ** $p \leq 0.01$; * $p \leq 0.05$; NS = not significant ($p > 0.05$)

Table 5.2 Prevalence of varicose veins and chronic venous insufficiency (CVI) in the right and left legs

	Grade	Right leg		Left leg		p value
		%	(n)	%	(n)	
Trunks	1	23.3	(365)	22.8	(357)	NS
	2	3.6	(57)	3.6	(56)	NS
	3	0.3	(5)	0.4	(6)	NS
Hyphenwebs	1	78.3	(1226)	80.3	(1257)	NS
	2	5.9	(93)	5.0	(79)	NS
	3	0.2	(3)	0.2	(3)	NS
Reticulars	1	78.1	(1223)	79.4	(1243)	NS
	2	4.1	(64)	3.5	(55)	NS
	3	0	(0)	0	(0)	-
CVI	1	4.7	(73)	4.6	(72)	NS
	2	1.1	(17)	1.0	(15)	NS
	3	0.2	(3)	0.5	(8)	NS

Footnote:

- (n) = number in each group with varices/CVI
- NS = not significant ($p > 0.05$)

Table 5.3 Prevalence of trunk varices (grades 1-3) by age and sex

	Age (years)								Total (age-adjusted)					
	18-24	25-34	35-44	45-54	55-64	%		(n)						
Males	20.0	15.5	36.1	42.0	61.4	39.7	(11)	(16)	(57)	(76)	(124)			
Females	5.3	13.9	22.6	41.9	50.5	32.2	(4)	(22)	(42)	(95)	(111)			
Total	11.5	14.6	28.8	41.9	55.7	31.8	(15)	(38)	(99)	(171)	(235)			

Footnote:

- (n) = number in each group with varices

Figure 5.1 Prevalence of chronic venous insufficiency (CVI) by age and sex

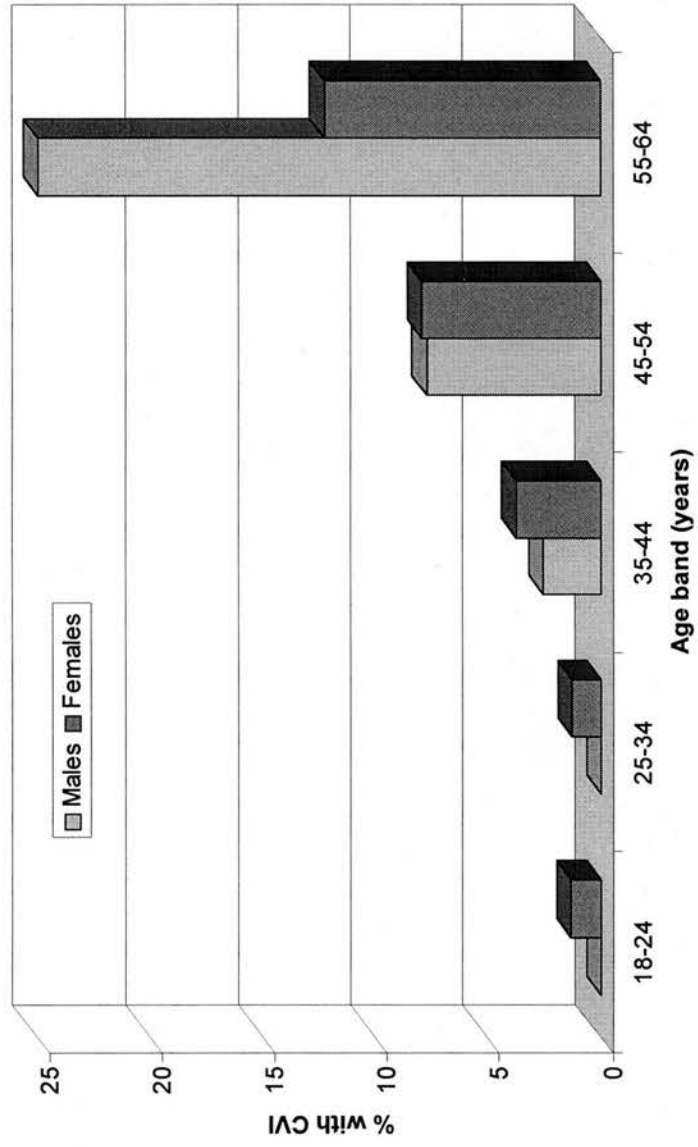


Table 5.4 Age- and sex-adjusted prevalence of trunk varices (grades 1-3) and chronic venous insufficiency (CVI) (grades 1-3) according to social class

Social Class	Trunk varices		CVI	
	%	(n)	%	(n)
I	35.0	(43)	5.6	(6)
II	35.8	(185)	7.5	(39)
IIIN	32.2	(113)	7.0	(24)
IIIM	43.4	(91)	13.3	(29)
IV	33.4	(33)	10.1	(9)
V	40.0	(32)	8.1	(8)

Footnote:

- Social class based on occupation.
- (n)=number in each group with varices/CVI
- Based on a total (n)=1376. Excluded were housewives (n=123), students (n=56), armed forces (n=6), unemployed with no previous job (n=2) and missing data (n=3).

Figure 5.2(a) Prevalence of trunk varices (unadjusted and age-adjusted figures) by sex-specific quartiles of body mass index (BMI)

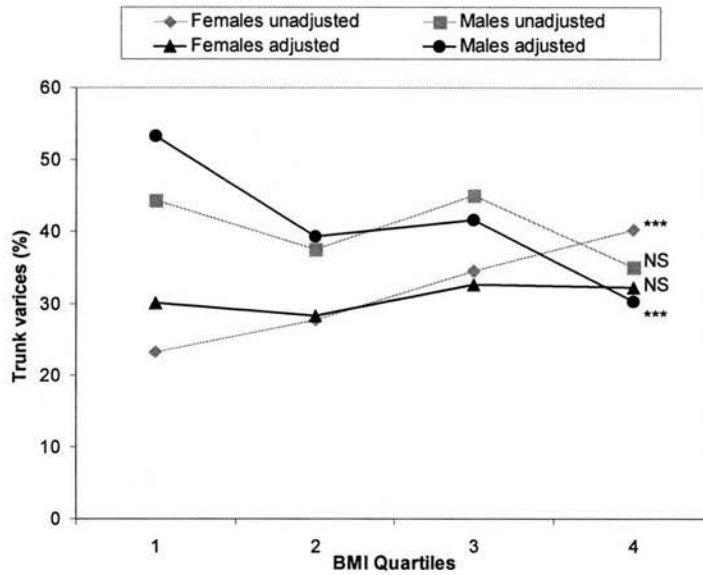
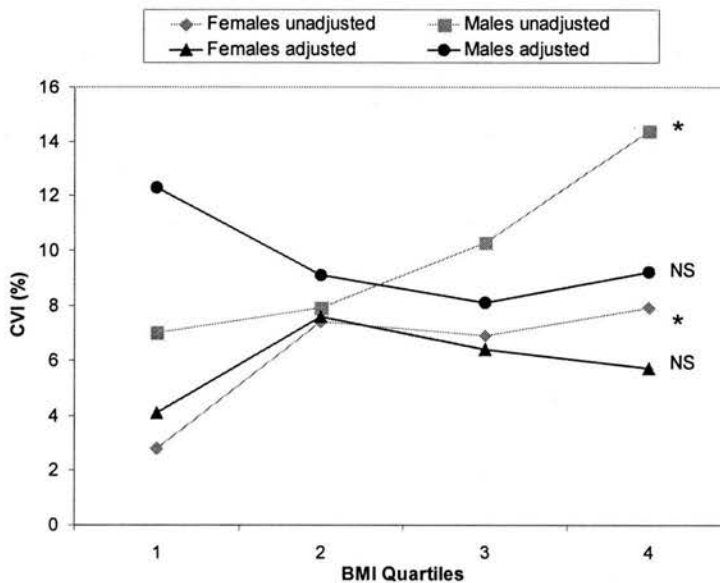


Figure 5.2(b) Prevalence of chronic venous insufficiency (unadjusted and age-adjusted figures) by sex-specific quartiles of body mass index (BMI)



Footnote:

- Test for linear trend across BMI quartiles *** $p \leq 0.001$; * $p \leq 0.05$; NS = not significant ($p > 0.05$)

Table 5.5 Kappa values for agreement of the two methods of classification of venous status in the Edinburgh Vein Study for right leg, left leg and individual subjects

(a) Agreement for classifying presence/absence of disease

	Right leg	Left leg	Per subject
Trunks	0.65	0.63	0.67
Hyphenwebs	0.40	0.40	0.36
Reticulars	0.40	0.43	0.44
CVI	0.70	0.69	0.71

(b) Agreement for classifying grades of disease (grades 1–3)

	Right leg	Left leg	Per subject
Trunks	0.60	0.57	0.60
Hyphenwebs	0.38	0.39	0.38
Reticulars	0.35	0.37	0.39
CVI	0.66	0.61	0.64

Footnote:

- The two methods of classification were based on (i) examination of the subject in the clinic and (ii) analysis of the colour photographic slides
- To calculate a score for individual subjects, the leg with the higher grade was taken as the subject's score
- Interpretation of Kappa values (Fleiss 1981)
 - <0.40 = poor agreement;
 - 0.40-0.75 = fair to good agreement
 - ≥0.75 = strong agreement
- The ten subjects with grade 3 CVI were excluded from the comparison in Table 5(b), as they were classified for grade of disease according to history of leg ulcer.

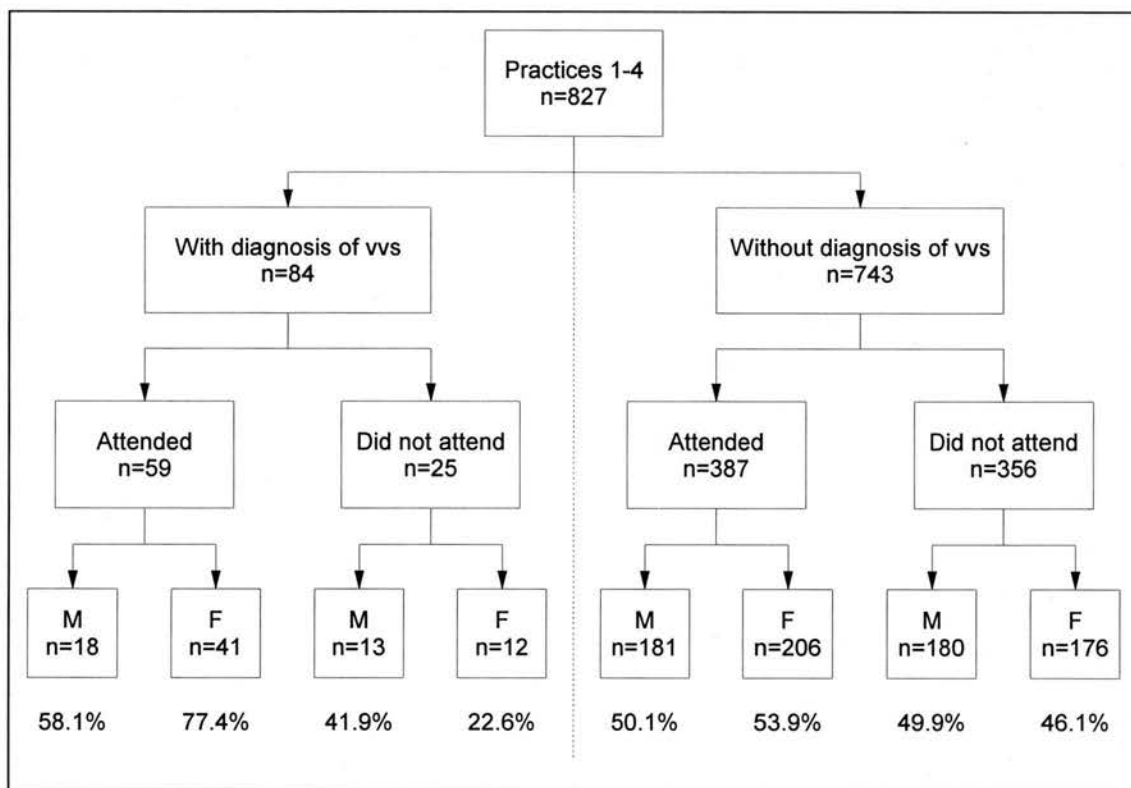
Table 5.6 Age-adjusted prevalence of varices and chronic venous insufficiency (CVI) according to sex, as classified by the 2 principal observers

Category (%)	Men			Women		
	Observer		p-value	Observer		p-value
	1	2		1	2	
Trunks	43.2	42.2	NS	31.2	33.1	NS
Hyphenwebs	85.8	86.1	NS	95.1	92.4	NS
Reticulars	88.0	84.3	NS	90.1	92.4	NS
CVI	11.5	10.1	NS	6.0	6.8	NS

Footnote:

- NS = not significant ($p > 0.05$)

Figure 5.3 Estimate of the proportion of men and women from Practices 1-4 with and without a doctor's diagnosis of varicose veins who attended the Edinburgh Vein Study



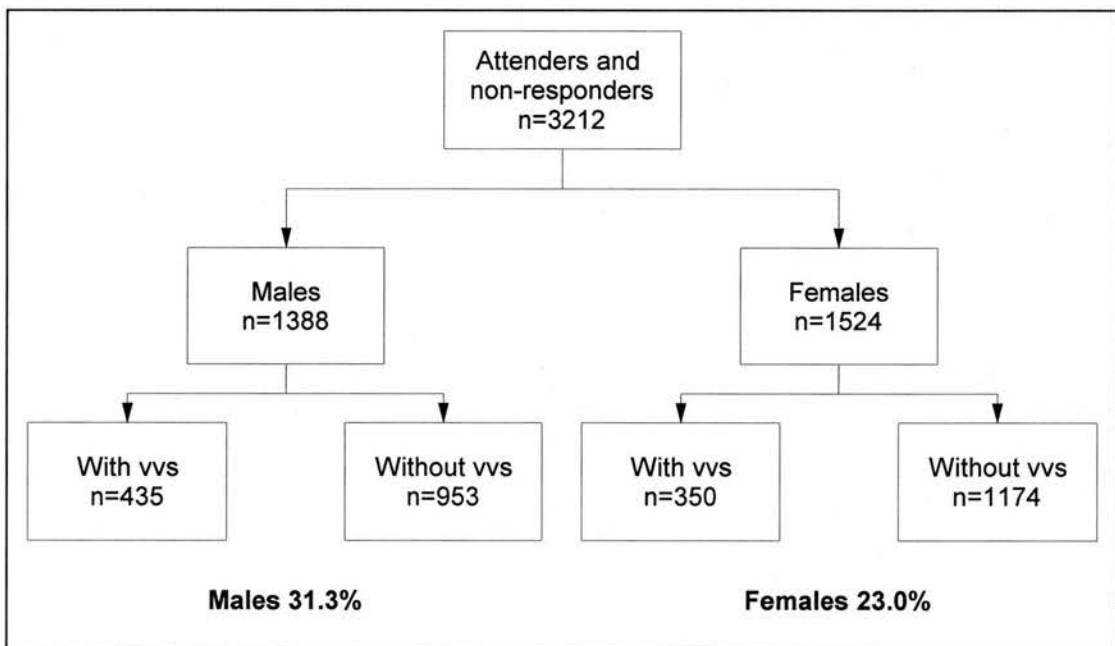
Footnote:

- Percentages refer to proportion who did/did not attend according to
 - individual sex (M=male, F=female)
 - presence or absence of diagnosis of varicose veins (vvs)
- Based on the sum of attenders plus non-responders for practices 1-4 (n=827)
- Based on age-adjusted prevalence of doctor's diagnosis of varicose veins (adjusted for difference in age between attenders and non-responders)
- Data from non-responders who replied to follow-up questionnaire extrapolated to all non-responders in practices 1-4

Table 5.7 Estimate of prevalence of varicose veins in non-responders

	Sex	Reported diagnosis of vvs	Prevalence of vvs	Total (n)	Total with vvs (n)
Attenders	M	10.0	^a 40.6	699	284
	F	17.1	^a 31.6	867	274
Non-responders	M	5.4	^b 21.9	689	^c 151
	F	6.2	^b 11.5	657	^c 76

Figure 5.4 Estimate of prevalence of varicose veins in total eligible population using data from Table 5.7



Footnote:

- vvs = varicose veins; M = male; F = female
- ^aobserved prevalence of trunk varicose veins on examination
- ^bestimated by extrapolating data from attenders according to the following formula (prevalence ÷ reported diagnosis) in attenders x reported diagnosis in non-responders
- ^cestimated as follows for each sex: (prevalence of vvs x total) in non-responders
- in all instances raw data used, unadjusted for age

CHAPTER 6

RESULTS III

VENOUS REFLUX

6.1 INTRODUCTION

Duplex scanning has become the method of choice for the investigation of venous reflux (Porter et al. 1995). It combines the assessment of anatomic structure and the functional evaluation of blood flow (Thibault 1995) to enable quantification of reflux duration in specific superficial and deep vein segments (Porter et al. 1995). This chapter presents the duplex scanning results from the Edinburgh Vein Study population and describes the prevalence and patterns of venous reflux in individual vein segments. The relationship between reflux and venous disease status is explored comparing two different cut-off points to define significant reflux. Finally the association between venous reflux and the presence of varicose veins and CVI is examined.

6.2 PREVALENCE OF VENOUS REFLUX

6.2.1 Prevalence of reflux in individual vein segments

Table 6.1 shows the prevalence of reflux of ≥ 0.5 seconds duration ($RD \geq 0.5$) and > 1.0 second duration ($RD > 1.0$) for each vein segment in right and left legs separately, and

in both legs together. (In addition, a dual superficial femoral vein was visualised in 471 subjects in the right leg, 458 subjects in the left leg and 277 subjects in both legs, but in each leg only 2 subjects (0.4%) showed $RD \geq 0.5$ in this vein.) There was no significant difference in the prevalence of reflux in any individual segment between the right and left legs for either $RD \geq 0.5$ or $RD > 1.0$ (all $p > 0.05$). The lower thigh LSV segment most often showed reflux compared to all other deep and superficial vein segments examined, with 18.6% of subjects having $RD \geq 0.5$ at this segment in the right leg, 17.5% in the left leg and 8.0% in both legs. (Only 1241 of the 1566 subjects had valid results for SSV segments in both legs. If a short saphenous vein could not be visualised or confidently identified as such, it was recorded as a missing value rather than assuming that there was no reflux present in the SSV.) Among the deep vein segments, the above knee popliteal segments most often showed reflux. In the superficial vein segments, there was little difference between the proportion of subjects with $RD \geq 0.5$ and $RD > 1.0$. However in the different deep vein segments, the prevalence of $RD \geq 0.5$ was 2 to 4 times higher than the prevalence of $RD > 1.0$.

6.2.2 Distribution and duration of reflux

The proportion of subjects showing any reflux in the individual vein segments were very similar in the right and left legs. The highest prevalence of 'any reflux' was in the popliteal vein, with 79% of all individual popliteal vein segments exhibiting some reflux. Further analysis of all vein segments exhibiting 'any reflux' revealed that the median duration of reflux was highest in the CFV segments; right CFV, median=0.24 seconds (inter-quartile range 0.13 to 0.40); left CFV, median=0.24

seconds (inter-quartile range 0.13 to 0.41). Among those vein segments exhibiting 'any reflux', the widest range of reflux duration was seen in the lower thigh LSV segments; right lower thigh LSV, median=0.13 seconds (inter-quartile range 0.10 to 2.05); left lower thigh LSV, median=0.13 seconds (inter-quartile range 0.10 to 2.25).

6.2.3 Prevalence of turbulent flow

Presence of turbulence was recorded in less than 2.5% of subjects at each vein segment apart from the CFV segments, where it was documented in 8.0% of subjects on the right leg and 9.8% of subjects on the left leg.

6.2.4 Prevalence of reflux by sex

Figure 6.1 compares the age-adjusted prevalence in men and women of $RD \geq 0.5$ in either leg, at individual vein segments. For all deep vein segments, men had a higher prevalence of reflux than women. This sex difference reached statistical significance in all deep vein segments except the upper SFV. Conversely, women had a higher prevalence of reflux in the superficial vein segments, although the sex differences in these segments were not statistically significant (all $p > 0.05$). If more women than men had had their incompetent superficial veins surgically removed, resulting in missing values for some superficial vein segments, that would have led to a misleading reduction in this sex differential. Therefore, subjects who had missing values for individual LSV segments on duplex scanning and who also reported having had previous varicose vein surgery were identified. Even assuming that all these subjects would have had $RD \geq 0.5$ in the missing LSV segments, the sex

differential for reflux in the upper and lower thigh LSV segments did not attain statistical significance (both $p>0.05$).

For $RD>1.0$ men continued to have a higher prevalence than women of reflux in the lower SFV ($p\leq 0.01$) and the below knee popliteal ($p\leq 0.05$) segments. However, for $RD>1.0$ the sex differential for the above knee popliteal segment decreased ($p>0.05$) and in the CFV and upper SFV segments, the proportions of men and women with $RD>1.0$ were almost identical; CFV, 3.7% of men and 3.5% of women; upper SFV, 2.2% of men and 2.3% of women (both $p>0.05$). For $RD>1.0$, women had a higher prevalence of reflux in their superficial vein segments than men, although again the sex differences were not significant.

6.2.5 Prevalence of reflux by age

In many of the vein segments, there was a general trend towards a higher prevalence of reflux in the older age groups. Figure 6.2 shows the proportion of subjects with $RD\geq 0.5$ and $RD>1.0$ in the lower thigh LSV segment of either leg, by age group. A highly significant linear association between prevalence of reflux and age was noted for both $RD\geq 0.5$ and $RD>1.0$ (both $p\leq 0.001$).

6.3 PATTERNS OF REFLUX

Table 6.2(a) shows the patterns of reflux in the femoral and long saphenous veins. In the right leg, 7.4% of subjects had $RD\geq 0.5$ in the CFV segment, 2.0% in both the

CFV and upper LSV segments, and 1.1% in both the CFV and upper SFV segments. Only 0.5% of subjects had $RD \geq 0.5$ in all three vein segments. The results were similar for the left leg. For $RD > 1.0$, in each leg 2.0% of subjects had reflux in the CFV segment and 0.3% had reflux in all three segments. Table 6.2(b) shows patterns of reflux in the popliteal and short saphenous vein system. In the right leg, 12.5% of subjects had $RD \geq 0.5$ in the above knee popliteal segment, 1.0% in both the above knee popliteal and SSV segments, and 5.7% in both the above knee and below knee popliteal vein segments. Only 1.3% had reflux in all 3 vein segments. The prevalences were slightly lower for the left leg, and approximately halved for $RD > 1.0$.

6.4 RELATIONSHIP BETWEEN REFLUX AND 'VENOUS DISEASE'

6.4.1 Venous disease status

For the purposes of the following discussion, subjects were classified as follows; the group with 'no disease' comprised those subjects with no trunk varices, CVI, 'perforators' or history of varicose vein treatment, and a maximum of grade 1 hyphenweb and/or reticular varices; the group with 'venous disease' included all subjects with trunk varices and/or CVI.

According to these definitions, 861 subjects (516 women and 345 men) had 'no disease' and 579 subjects (282 women and 297 men) had 'venous disease'. The remaining 126 subjects fell into neither category (due to having either 'perforators', previous varicose vein treatment, and/or grade 2/3 reticulars/hyphenwebs without

trunks or CVI) and are excluded from this analysis. Of the 642 men in the analysis, 46.3% had 'venous disease' compared to 35.3% of the 798 women ($p \leq 0.001$). Those subjects with 'venous disease' were significantly older than those with 'no disease' (mean age 51.2 years compared with 40.4 years) ($p \leq 0.001$).

6.4.2 Prevalence of reflux by disease status

The relationship between reflux and overall venous disease in a subject will be considered in this section. Section 6.5 will relate reflux to specific categories of disease in individual limbs.

Figure 6.3 shows the age- and sex-adjusted prevalence of $RD \geq 0.5$, at individual vein segments in either leg, by disease status. The prevalence of reflux was significantly higher at each vein segment in subjects with 'venous disease' (all $p \leq 0.001$). Of the 630 'disease free' subjects with complete duplex data for all 16 vein segments, 411 (65%) had no evidence of $RD \geq 0.5$ in any segment. For $RD > 1.0$, the prevalence of reflux was also significantly higher at each vein segment in those with 'venous disease' (all $p \leq 0.001$), although there were very few subjects with 'no disease' who had $RD > 1.0$ in the common femoral vein or superficial femoral vein segments of either leg. (CFV $n=4$, 0.5%; SFV upper $n=3$, 0.4%; SFV lower $n=8$, 1.0% (percentages are age- and sex-adjusted)). Of the 630 'disease free' subjects described above, 518 (82%) had no evidence of $RD > 1.0$ in any vein segment.

6.4.3 Distribution and duration of reflux by disease status

Table 6.3 presents the distribution of reflux in individual vein segments in those with and without 'venous disease'. For each patient, the value was taken from the leg which showed the longer duration of reflux for each vein segment. Although there was considerable overlap in duration of reflux in individual vein segments between the two groups, for all segments the median, 75th and 95th percentiles were higher in those with 'venous disease'. In those with 'no disease', the 75th percentiles were all less than 0.50 seconds. The 95th percentiles for the upper LSV and SSV segments were less than 0.50 seconds and for all other vein segments were less than 1.00 second, apart from the lower thigh LSV segment (6.46 seconds). When analysed according to sex, the difference between the median for men and women with 'no disease' was no more than 0.05 seconds for any segment. In those subjects with 'venous disease', the median was highest for the lower thigh LSV segment (2.30 seconds). The 75th percentiles for the CFV, upper and lower SFV and SSV segments were all less than 0.50 seconds. Only the 75th percentiles for the upper and lower thigh LSV segments were greater than 1.00 second (4.30 and 6.97 seconds respectively). All of the 95th percentiles were greater than 1.00 second in those with 'venous disease'. The sex differences in the median duration of reflux in those with 'venous disease' were no more than 0.08 seconds for any segment, apart from for the LSV segments. In those with 'venous disease', the median (inter-quartile range) for duration of reflux in the upper LSV segment was 0.26 (0 - 5.14) for women and 0.13 (0 - 2.04) for men, and for the lower thigh LSV segment was 4.14 (0.12 - 8.00) for women compared to 0.23 (0.09 - 6.08) for men.

6.4.4 Cut-off point for significant reflux

The relationship between duration of venous reflux in certain segments and the presence of 'venous disease' in a subject was examined further. The sensitivities and specificities were calculated when different cut-off points for duration of reflux were used as a test for 'venous disease'. The resulting receiver operator curves (ROC) for these calculations on the upper LSV and below knee popliteal vein segments are shown in Figures 6.4 (a) and (b) respectively. In the upper LSV segment, for a cut-off point of >0.5 seconds duration of reflux, the sensitivity was 38.0% and the specificity 97.2%, while for a cut-off point of >1.0 seconds duration of reflux, the sensitivity was 36.4% and the specificity 97.4%. In the below knee popliteal segment, for a cut-off point of >0.5 seconds duration of reflux, the sensitivity was 26.0% and the specificity 87.9%, while for a cut-off point of >1.0 seconds duration of reflux, the sensitivity was 14.2% and the specificity 95.7%.

6.5 RELATIONSHIP BETWEEN REFLUX AND VARICOSE VEINS AND CHRONIC VENOUS INSUFFICIENCY

As the prevalence of varices, CVI and venous reflux was similar in the right and left legs (Tables 5.2 and 6.1), the following results are presented for the right legs only. For the following analysis, reflux was defined as $RD \geq 0.5$.

6.5.1 Prevalence of reflux by grade of trunk varices

Table 6.4 shows the age-adjusted prevalence of reflux in individual vein segments of the right leg in men and women separately, according to grade of trunk varicose veins (none, grade 1, grade 2/3). In men, the prevalence of reflux increased in each vein segment with increasing severity of trunk varices (test for trend: $p \leq 0.001$ for all segments except the upper SFV ($p \leq 0.01$)). In women, the prevalence of reflux increased with severity of trunk varices, showing a highly statistically significant trend ($p \leq 0.001$) in all vein segments except the upper SFV ($p > 0.05$). The higher prevalence of reflux in the deep vein segments of men compared to women, as illustrated in Figure 6.1, persisted across the grades of trunk varices and was most apparent in the above knee popliteal segments: no trunks, 10.6% of men and 7.5% of women had reflux; grade 1 trunks, 20.4% of men and 17.6% of women had reflux; grade 2/3 trunks, 53.4% of men and 27.0% of women had reflux. Conversely, the trend towards a higher prevalence of reflux in women compared with men in the superficial vein segments was highlighted when subjects with grade 1 trunk varices were compared: upper LSV segment, 17.5% of men and 39.4% of women had reflux; lower thigh LSV segment, 31.7% of men and 52.1% of women had reflux; SSV segment, 6.6% of men and 9.1% women had reflux.

6.5.2 Prevalence of reflux by grade of hyphenweb and reticular varices

Table 6.5 shows the prevalence of reflux in individual vein segments according to grade of hyphenweb varices in the right leg, in men and women. In men, there was a significant increase in prevalence of reflux in the superficial vein segments with

increasing severity of hyphenwebs (test for trend: upper LSV and SSV $p \leq 0.05$, lower thigh LSV $p \leq 0.01$). In women, the only segment which showed a significant association between prevalence of reflux and grade of hyphenwebs was the upper SFV ($p \leq 0.05$). There was no significant association between grade of reticular varices and prevalence of reflux in either men or women (Table 6.6).

6.5.3 Association between reflux and chronic venous insufficiency

The numbers of men and women with the skin changes of more severe CVI (grade 2/3) in the right leg were small ($n=14$ and $n=6$ respectively). Therefore the prevalence of reflux in subjects with no signs of CVI was compared with the prevalence in those with any CVI (grades 1-3). Figure 6.5 illustrates the age-adjusted results for individual vein segments of right leg, for men and women combined. For each vein segment, there was a higher prevalence of reflux in subjects with signs of CVI ($p \leq 0.001$ for all vein segments except lower SFV and below knee popliteal (both $p \leq 0.01$)).

6.6 SUMMARY

There was no significant difference between the right and left legs in the prevalence of reflux in individual vein segments. The lower thigh LSV segment most often showed reflux. In the superficial vein segments, there was little difference between the proportion of subjects with $RD \geq 0.5$ and $RD > 1.0$. However in the different deep vein segments, the prevalence of $RD \geq 0.5$ was 2 to 4 times higher than the prevalence

of $RD > 1.0$ second. Men had a higher prevalence of reflux in the deep vein segments compared to women, a difference which reached statistical significance for $RD \geq 0.5$ in all deep vein segments except the upper SFV segment. Conversely, women had a (non-significantly) higher prevalence of reflux in the superficial vein segments. There was a trend towards a higher prevalence of reflux in the older age groups in many vein segments. The prevalence of reflux was significantly higher in subjects with 'venous disease' compared to those with 'no disease', but there was considerable overlap in duration of reflux in individual vein segments between these two groups. On analysis of the right leg and using $RD \geq 0.5$ to define reflux, the prevalence of reflux increased in individual vein segments with increasing severity of trunk varices in both sexes, but there was no consistent relationship between prevalence of reflux and grade of either hyphenweb or reticular varices. Subjects with any signs of CVI had a higher prevalence of reflux in all vein segments than subjects without CVI.

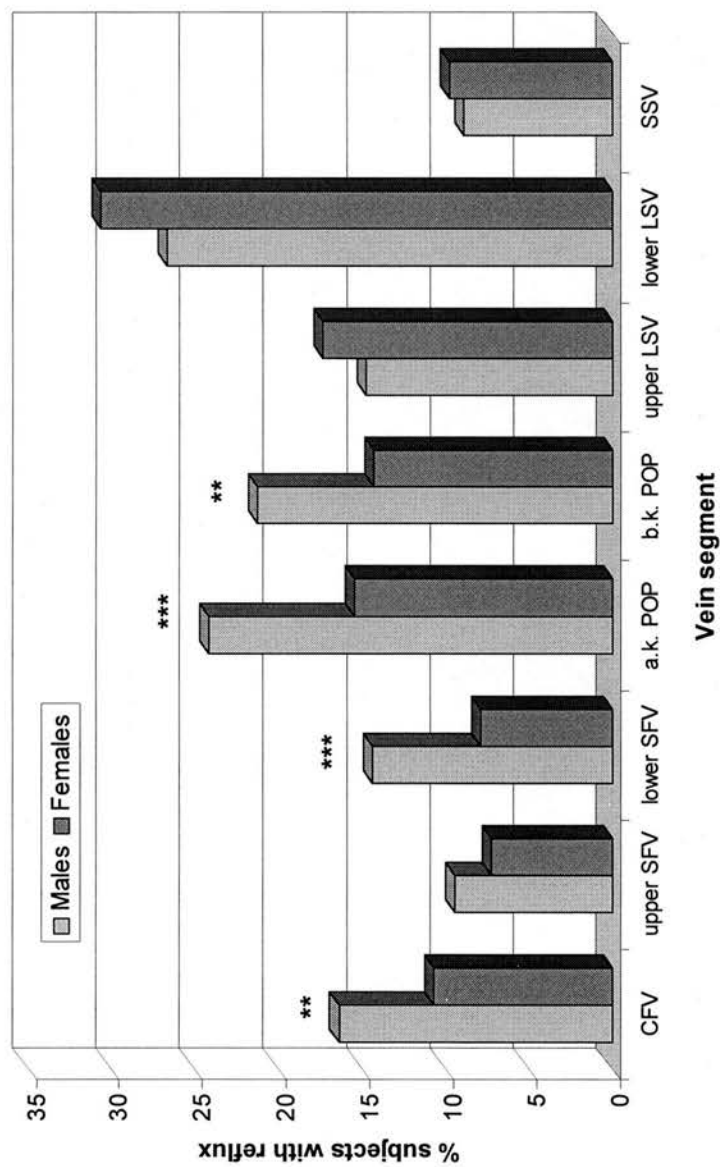
Table 6.1 Prevalence of reflux ≥ 0.5 seconds and >1.0 second duration in individual vein segments, legs separately and together

Vein segment	Right leg		Left leg		Both legs	
	Total ^a (n)	$\geq 0.5s$ %	Total ^a (n)	$\geq 0.5s$ %	Total ^b (n)	$\geq 0.5s$ %
CFV	(1542)	7.8	(1539)	8.0	(1539)	2.5
upper SFV	(1539)	5.2	(1540)	4.7	(1537)	1.7
lower SFV	(1539)	6.6	(1538)	6.4	(1536)	2.2
above knee popliteal	(1541)	12.3	(1541)	11.0	(1541)	3.9
below knee popliteal	(1540)	11.3	(1541)	9.5	(1540)	3.3
upper LSV	(1485)	10.0	(1477)	10.8	(1449)	4.8
lower thigh LSV	(1422)	18.6	(1432)	17.5	(1363)	8.0
SSV	(1342)	4.6	(1351)	5.6	(1241)	1.6
						1.1

Footnote:

- ^aReasons for missing values included: vein segment not visualised (eg. following vein stripping); absence of flow in vein segment; subjects unable to undergo all or part of the scan due to a pre-existing medical condition, feeling faint or the examination being performed in their home.
- ^bReflux in "both legs" calculated as a percentage of those subjects who had valid duplex measurements for that vein segment in both legs

Figure 6.1 Proportion of subjects with reflux ≥ 0.5 seconds duration in either leg at individual vein segments by sex (age-adjusted figures)



Footnote:

- a.k. POP=above knee popliteal; b.k. POP=below knee popliteal; lower LSV=lower thigh long saphenous vein
- *** $p \leq 0.001$; ** $p \leq 0.01$

Figure 6.2 Proportion of subjects with reflux ≥ 0.5 seconds and >0.1 second duration in the lower thigh segment of the long saphenous vein in either leg, by age

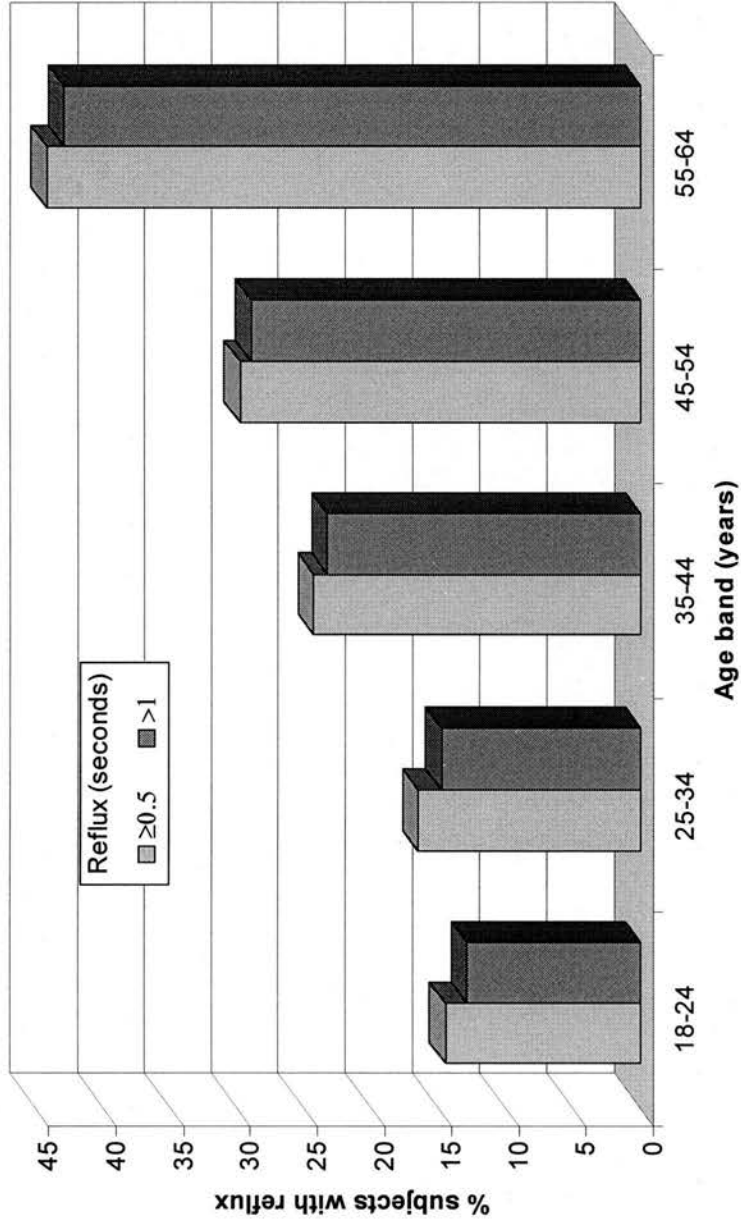


Table 6.2(a) Patterns of reflux in the femoral and long saphenous veins

Vein Segment	Right leg (n=1483)		Left leg (n=1476)	
	% with reflux		% with reflux	
	≥0.5s	>1.0s	≥0.5s	>1.0s
CFV (total)	7.4	2.0	7.5	2.0
CFV & upper LSV only	2.0	1.2	2.2	1.3
CFV & upper SFV only	1.1	0.1	0.9	0.1
CFV & upper SFV & upper LSV	0.5	0.3	0.5	0.3

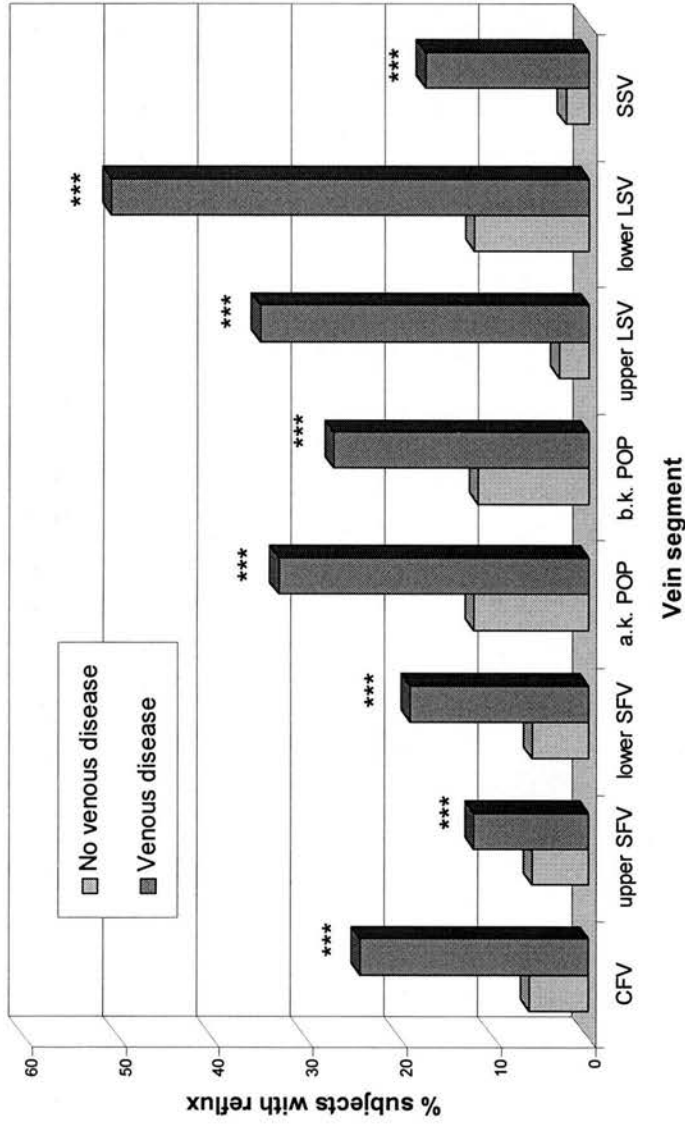
Table 6.2(b) Patterns of reflux in the popliteal and short saphenous veins

Vein Segment	Right leg (n=1341)		Left leg (n=1351)	
	% with reflux		% with reflux	
	≥0.5s	>1.0s	≥0.5s	>1.0s
above knee popliteal (total)	12.5	5.0	11.0	5.3
above knee popliteal & SSV only	1.0	0.6	0.8	0.5
above & below knee popliteal only	5.7	1.9	5.0	2.4
above & below knee popliteal & SSV	1.3	0.6	1.5	0.5

Footnote:

- (n) = number of subjects with complete duplex data for all relevant vein segments

Figure 6.3 Prevalence of reflux ≥ 0.5 seconds duration in either leg at individual vein segments, in subjects with and without 'venous disease' (age- and sex-adjusted figures)



Footnote

- a.k. POP=above knee popliteal; b.k. POP=below knee popliteal; lower LSV=lower thigh long saphenous vein
- *** $p \leq 0.001$;
- 'Venous disease'= trunk varices and/or CVI (see Section 6.4.1 for details)

Table 6.3 Distribution of reflux in individual vein segments, in those with and without 'venous disease'

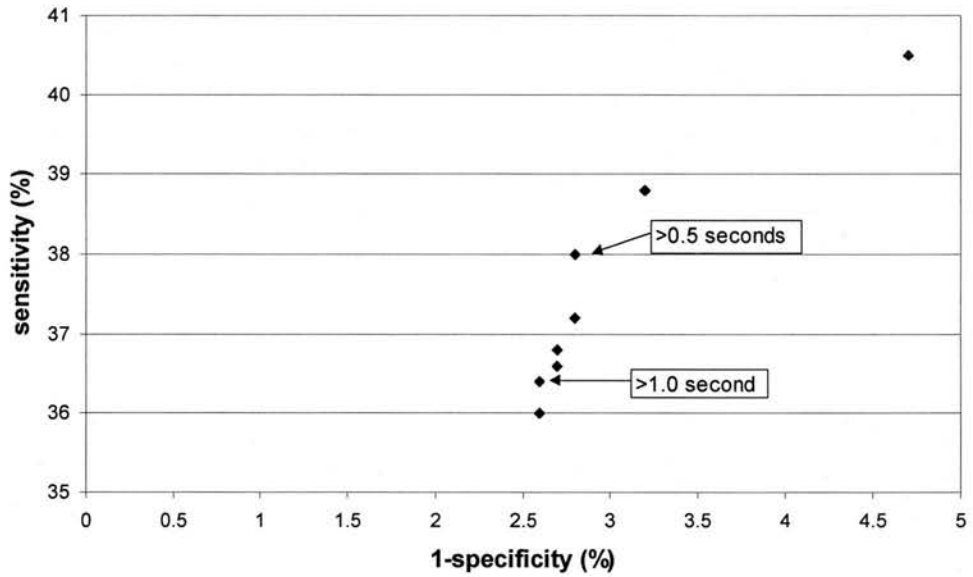
Segment ^a	No venous disease (n = 861)				Venous disease (n = 579)			
	Median	IQR	95th percentile	95th percentile	Median	IQR	95th percentile	95th percentile
CFV	0.09	0.00 - 0.26	0.54	0.54	0.18	0.00 - 0.48	1.63	1.63
upper SFV	0.11	0.00 - 0.25	0.52	0.52	0.15	0.00 - 0.33	1.14	1.14
lower SFV	0.13	0.04 - 0.25	0.53	0.53	0.18	0.06 - 0.40	2.88	2.88
above knee popliteal	0.17	0.10 - 0.32	0.84	0.84	0.25	0.13 - 0.68	2.63	2.63
below knee popliteal	0.14	0.10 - 0.28	0.88	0.88	0.20	0.12 - 0.53	2.30	2.30
upper LSV	0.00	0.00 - 0.10	0.29	0.29	0.15	0.00 - 4.30	8.00	8.00
lower thigh LSV	0.11	0.05 - 0.16	6.46	6.46	2.30	0.10 - 6.97	8.00	8.00
SSV	0.10	0.00 - 0.14	0.27	0.27	0.13	0.10 - 0.24	4.08	4.08

Footnote:

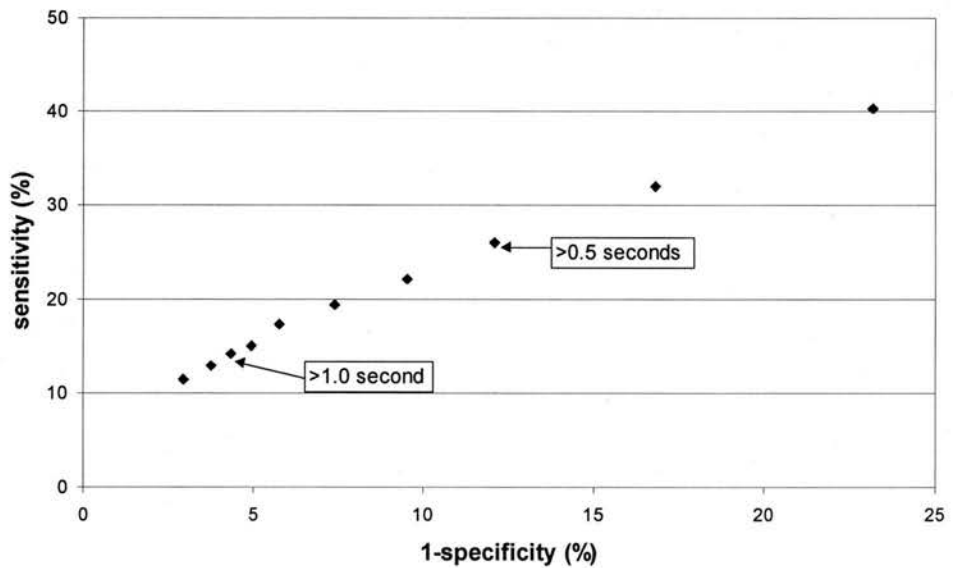
- ^a Value taken from the leg with the longer duration of reflux for each vein segment
- IQR = interquartile range (25th percentile – 75th percentile)
- 'Venous disease' = trunk varices and/or CVI (see Section 6.4.1 for details)

Figure 6.4 ROC curves showing the sensitivity and 1-specificity of different cut-off points for significant reflux in different vein segments, as a measure of the presence or absence of 'venous disease'.

(a) Upper long saphenous vein segment



(b) Below knee popliteal vein segment



Footnote:

- Cut-off points from >0.3 seconds to >1.2 seconds illustrated
- 'Venous disease'= trunk varices and/or CVI (see Section 6.4.1 for details)

Table 6.4 Prevalence of reflux (≥ 0.5 seconds) in individual vein segments of the right leg, by grade of trunk varices

	Men (%)			Women (%)			p value
	None (n=476)	Grade 1 (n=191)	Grade 2/3 (n=32)	None (n=663)	Grade 1 (n=174)	Grade 2/3 (n=30)	
CFV	7.0	11.7	34.1	3.9	11.3	31.8	***
upper SFV	4.5	9.7	14.2	3.6	6.1	7.6	NS
lower SFV	5.5	13.1	24.5	3.5	8.6	14.0	***
above knee popliteal	10.6	20.4	53.4	7.5	17.6	27.0	***
below knee popliteal	11.1	18.4	36.1	6.5	15.7	24.3	***
upper LSV	2.2	17.5	65.7	1.4	39.4	66.0	***
lower thigh LSV	7.1	31.7	80.1	8.5	52.1	69.5	***
SSV	1.3	6.6	21.9	2.9	9.1	27.7	***

Footnote:

- (n) = total number of subjects in each disease group. For each individual vein segment, proportions are calculated from the number of subjects with a valid duplex measurement
- Proportions by grade of trunk varices are adjusted for age across the grades, for each sex separately
- p-values refer to test for trend across the grades of varicose veins: *** $p \leq 0.001$; ** $p \leq 0.01$; NS = not significant ($p > 0.05$)

Table 6.5 Prevalence of reflux (≥ 0.5 seconds) in individual vein segments of the right leg, by grade of hyphenweb varices

	Men (%)			Women (%)			p value
	None (n=144)	Grade 1 (n=519)	Grade 2/3 (n=36)	None (n=100)	Grade 1 (n=707)	Grade 2/3 (n=60)	
CFV	11.6	8.8	11.8	5.9	5.6	15.5	NS
upper SFV	8.0	5.7	11.0	4.1	3.4	15.0	*
lower SFV	10.8	7.0	20.9	5.4	4.4	9.6	NS
above knee popliteal	16.4	13.4	32.1	10.9	9.7	13.9	NS
below knee popliteal	13.5	13.9	22.2	7.4	9.1	8.0	NS
upper LSV	5.1	8.9	17.8	11.8	10.7	11.2	NS
lower thigh LSV	10.0	18.2	32.7	19.1	19.3	16.7	NS
SSV	1.1	4.1	8.4	2.7	5.0	7.5	NS

Footnote:

- (n) = total number of subjects in each disease group. For each individual vein segment, proportions are calculated from the number of subjects with a valid duplex measurement
- Proportions by grade of hyphenweb varices are adjusted for age across the grades, for each sex separately
- p-values refer to test for trend across the grades of varicose veins: ** $p \leq 0.01$; * $p \leq 0.05$; NS = not significant ($p > 0.05$)

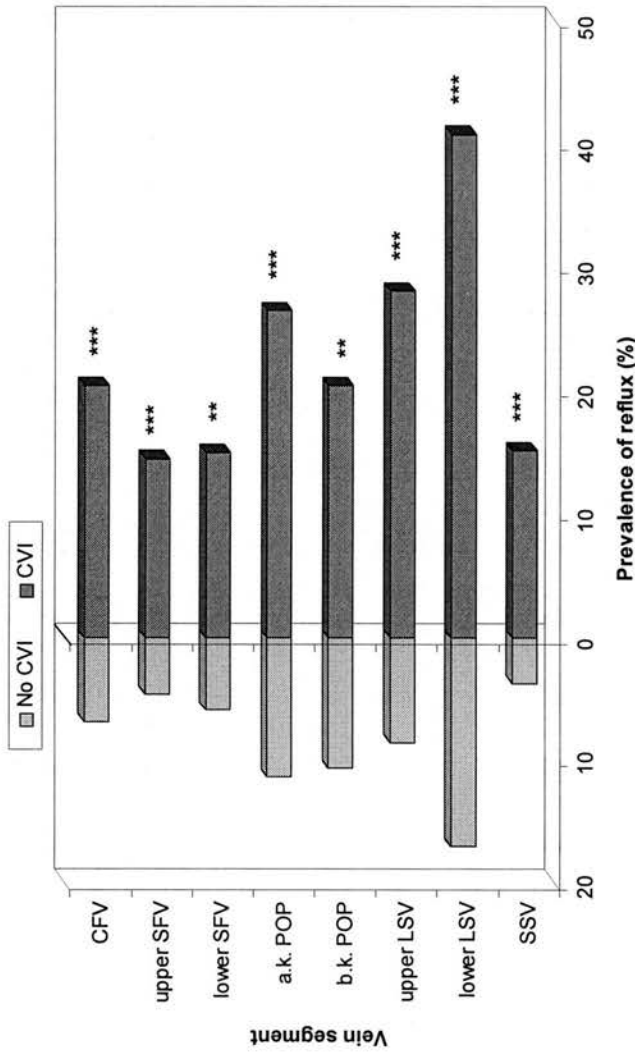
Table 6.6 Prevalence of reflux (≥ 0.5 seconds) in individual vein segments of the right leg, by grade of reticular varices

	Men (%)			Women (%)			p value (trend)	p value (trend)
	None (n=163)	Grade 1 (n=512)	Grade 2 (n=24)	None (n=116)	Grade 1 (n=711)	Grade 2 (n=40)		
CFV	9.1	9.2	19.5	3.0	6.7	11.1	NS	NS
upper SFV	8.2	6.2	3.7	5.7	3.8	5.8	NS	NS
lower SFV	7.6	8.6	14.4	4.6	4.6	9.9	NS	NS
above knee popliteal	18.5	13.5	24.0	8.3	10.4	9.9	NS	NS
below knee popliteal	17.8	13.6	7.7	9.1	8.9	7.6	NS	NS
upper LSV	8.1	9.2	3.9	9.1	11.2	9.9	NS	NS
lower thigh LSV	17.5	18.4	7.8	17.5	19.5	18.7	NS	NS
SSV	2.7	4.2	6.7	3.5	5.1	7.9	NS	NS

Footnote:

- (n) = total number of subjects in each disease group. For each individual vein segment, proportions are calculated from the number of subjects with a valid duplex measurement
- Proportions by grade of reticular varices are adjusted for age across the grades, for each sex separately. No subjects had grade 3 reticular varices.
- p-values refer to test for trend across the grades of varicose veins: NS = not significant ($p > 0.05$)

Figure 6.5 Prevalence of reflux (≥ 0.5 seconds) in individual vein segments of the right leg, by presence or absence of chronic venous insufficiency (CVI)



Footnote

- Based on the following right leg totals:- 'No CVI' n=1473 (men, n=644; women, n=829); 'CVI' n=93 (men, n=55; women, n=38). For individual vein segments, proportions are calculated from the number of subjects with a valid duplex measurement
- a.k. POP=above knee popliteal; b.k. POP=below knee popliteal; lower LSV=lower thigh long saphenous vein
- *** $p \leq 0.001$; ** $p \leq 0.01$

CHAPTER 7

DISCUSSION

7.1 INTRODUCTION

Many previous studies of venous disease have been carried out on populations which are not representative of the general population and estimates of the prevalence of venous disease vary widely. The purpose of the Edinburgh Vein Study was to determine the prevalence of varicose veins, CVI and venous reflux in a general population sample, with the long term aim of following the population up to determine the natural history and progression of these conditions. The study provides new information on the epidemiology of venous disease in the general population and is the first to use duplex scanning to assess venous function in a randomly selected adult population sample. This chapter starts by discussing some of the limitations of the study, including aspects of the methods and the response rate. It then proceeds to explore the main findings from the study and relate them to the current knowledge from previous studies of venous disease. Finally, the public health implications of venous disease are considered.

7.2 LIMITATIONS OF THE METHODS

7.2.1 Classification of venous disease

Although other classifications of CVI were available at the time of planning the study (Porter et al. 1988), the classification of venous disease from the Basle Study (Widmer 1978) was used as it was considered to be the best available at the time (Callam 1994) for classifying the different degrees of varicose veins. In addition, the use of colour photographic slides provide a permanent record of venous status at baseline for use in follow-up studies. The CEAP clinical classification for chronic venous disease is an attempt to standardise the reporting of venous disease (Porter et al. 1995) but was not developed until the Edinburgh Vein Study was already underway. However, the Basle Study classification of CVI can be converted relatively easily into the CEAP clinical categories as required, if the latter becomes accepted as the standard method of classification (Section 3.4.4).

7.2.2 Measurement of venous function

The measurement of duration of reflux in individual vein segments has become an accepted method of determining the presence of venous incompetence. The method used in the Edinburgh Vein Study followed work on the assessment of repeatability of duplex scanning for use in epidemiological studies (Evans et al. 1995). This work suggested that repeatability was reasonable at certain sites but was influenced by the position of the vein, and by observer training and experience. As a result of these findings, certain measures were taken prior to and during the Edinburgh Vein Study

to enhance reproducibility; protocols were set up detailing the measurement technique, the two main observers were initially trained together in the method, and periodically throughout the study, sequential duplex scans were performed by all three observers on the same volunteers as a method of quality control.

It was recognised that by not scanning the calf veins, some questions in this study would be left unanswered. However, on balance it was considered that duplex scanning of the calf and perforator veins would be difficult, time-consuming and of doubtful accuracy, when using a non-colour Doppler system in a population of over 1500 subjects. Duplex scanning, which provides information on the functioning of individual vein segments, would have ideally been combined with a global measure of venous function of the lower limb such as photo- or air-plethysmography. The combination of air-plethysmography and duplex ultrasonography has been judged to provide the best means of assessing venous reflux (Bays et al. 1994). However, it was considered that extending the appointment duration in the Edinburgh Vein Study much beyond one hour would be less acceptable to a population of working age, and would risk further jeopardising the response rate. Therefore, it was decided to limit the assessment of venous function to duplex scanning of the vein segments already described.

7.2.3 Response

The Edinburgh Vein Study examined a randomly selected population sample aged 18-64 years. The relatively young age range of the population was selected in order to

allow the investigation of early venous disease and to follow through the natural history of venous insufficiency in the cohort from an early stage. The final response rate was 53.8%, which illustrates one of the problems of carrying out a survey on a general population sample, namely the difficulty in recruiting a young, mobile, working population to investigate a condition which has a low profile and is not life threatening. One alternative would have been to investigate venous disease in a specific population or occupational group where a more 'captive' target population would have been likely to yield a much higher response rate. However, much would have been lost in such an approach as the final results would have had limited application to the general population. Furthermore, in the Edinburgh Vein Study, a concerted effort was made to obtain a representative sample of the city's population by involving participation from general practices situated in the most deprived areas of the city and not simply those in more affluent areas where the response rate would have been higher.

The final response rate was calculated by excluding from the target population total all those subjects identified during the study as having moved from the area ('returns'), and all those subjects who were not contacted despite repeated efforts to do so ('unreachables'). The 'returns' represented inaccuracies in the sampling frame rather than additional non-responders, and therefore it seemed justifiable to exclude them from the denominator in the calculation of the final response rate (Diamond 1995). 'Unreachables' were so classified after no response was received to two letters of invitation and at least three attempts at telephone contact, where a telephone number was available. It could be argued that some of the 'unreachables' may have received their invitations to participate in the study but chose not to reply, in which case they

should have been classed as non-responders and not excluded from calculation of the response rate. In a previous study which sent questionnaires to a random sample of 18-75 year olds selected from a general practice register in Stockport, it was shown that 22% of patients were unlikely to have received their mailed questionnaire as they were not living at the address on the register (Pope and Croft 1996). If 22% of the Edinburgh Vein Study population had failed to receive their invitation and were therefore excluded from the calculation, the response rate would have been approximately 47.7%. Although it is difficult to define the precise figure, the true response rate of those contacted and living in the area must lie between 44.9% (the figure obtained if all of the 'unreachables' received their invitation) and 53.8% (if none of the 'unreachables' received their invitation).

7.3 PREVALENCE OF VENOUS DISEASE

7.3.1 Varicose veins

Results from the Edinburgh Vein Study confirm that venous disease is common in the general population, with approximately one third of the study population showing some degree of trunk varicose veins. In addition, the vast majority of subjects had a mild degree of hyphenweb and reticular varices, suggesting that these minor stigmata are 'the norm'. An increase in varices with age was demonstrated, in common with findings from many other studies (Callam 1994).

Differences in the age and sex composition of populations from previous studies contribute to the wide variation in the reported prevalence of varicose veins and make it difficult to compare different studies' results. In an attempt to compare the

results from the Edinburgh Vein Study with those from other similar study populations, the prevalence of varicose veins obtained from general population surveys are shown in Table 7.1. Two of these surveys used self-administered questionnaires to assess the prevalence of varicose veins, one relying on the subject's own observation (Franks et al. 1992) and the other on a physician's previous diagnosis of varicose veins (Sisto et al. 1995). The other studies examined subjects for presence of varicose veins (Coon et al. 1973, Abramson et al. 1981). The age range differed among the study populations and only three of the five reported age-adjusted results (Abramson et al. 1981, Sisto et al. 1995 and the Edinburgh Vein Study). Despite this, the prevalence of varicose veins in women was similar in all five studies, ranging from 25-32%. However, the prevalence in men varied widely from 7% (Sisto et al. 1995) to 40% in the Edinburgh Vein Study. The particularly low value in the former study was based on reported physician's diagnosis and may reflect a reluctance by men to consult their doctor about varicose veins.

7.3.2 Sex differences

The major unexpected finding from the Edinburgh Vein Study was the significantly higher prevalence of trunk varicose veins in men compared to women. This significant difference was largely due to a higher prevalence of mild (grade 1) varices in men. Men also had a higher prevalence of CVI (grades 1-3) than women, although the sex differences were not significant when grades of CVI were analysed individually. Conversely, women had a higher prevalence of moderate (grade 2) hyphenweb and reticular varices, and of pitting ankle oedema, than men.

Most of the evidence from previous studies of varicose veins indicates a higher prevalence in women, although the magnitude of the difference varies between studies (Table 2.3). It has been suggested that variation in the sex ratio may be partly due to differences in the age of the populations studied and the methods of measurement used (Callam 1994). Many of the results on overall prevalence from previous studies were not adjusted for age, and this factor may have obscured any true sex differences. For example, the Basle Study (the origin of the method of classification used for the Edinburgh Vein Study) found a similar prevalence of all varices in men (56%) and women (55%). However, when the results were adjusted for age, the prevalence decreased to 54.8% in men and increased to 61.2% in women ($p < 0.001$) (Widmer 1978). Regarding methods of measurement, studies which relied on self-assessment of varicose veins or reporting of a previous diagnosis by a physician may have been prone to an alternative bias, because women may have been more likely to report varices or to consult their doctor for this condition than men. This hypothesis is supported by the Edinburgh Vein Study. The prevalence of previous doctor diagnosed varicose veins reported in the study questionnaire was 10% in men compared to 17% of women but men were subsequently found to have a significantly higher prevalence of trunk varices than women on examination.

There are several studies which have not found a higher prevalence of varicose veins in women. Beaglehole et al. (1975) found no significant sex differences in the age-standardised prevalence rates of varices in the Cook or Tokelau Islanders from the South Pacific. In a study of villagers in New Guinea, only one woman was found

to have varicose veins, resulting in a prevalence of varices of 0.1% in women compared to 5.1% in men (Stanhope 1975). There was no significant difference in the prevalence of varices between men (mean age 73.4 years) and women (mean age 74.2 years) examined in a Turkish study (34.5% versus 38.3% respectively) (Komsuoglu et al. 1994).

However, the small number of surveys which have studied population samples have all found a higher prevalence of varices in women than men. Abramson et al. (1981) surveyed residents of a Jewish neighbourhood of Western Jerusalem and found that the age standardised prevalence for varicose veins (excluding venectasias) was 29.5% in women and 10.4% in men (Table 7.1). The Tecumseh Community Health Study (Coon et al. 1973) was a longitudinal study of a total USA community. Although the overall prevalence of 'any varicose veins' for men and women shown in Table 7.1 was not age standardised, the prevalence of varices was higher for women in each age group in this study. In a random sample of men and women over 65 years of age from Southern Italy, the prevalence of varicose veins (defined as 'any reticular or truncal visible varicosities of the lower limb') was 35.2% in women and 17% in men (Canonica et al. 1998). Leipzig et al. (1989) examined a sample of 2821 subjects aged 45-65 years, randomly selected from the greater Aachen district and found the prevalence of varicose veins to be 29.0% in women and 14.5% in men.

Yet, in a recent study in South Wales in which 560 randomly selected men and women over the age of 60 years were examined, female sex was a significant risk factor for CVI but not for varicose veins (I. Harvey, personal communication). In

another recent study in Bochum, Germany, children were examined on three occasions during their school education. By the age of 18-20 years, males had a higher prevalence of trunk varices, tributary varices and incompetent perforators than females, while females had a higher prevalence of reticular varices and telangiectasias (hyphenwebs) (Schultz-Ehrenberg et al. 1992). Although no tests of significance were reported on these results, the gender differences followed a similar pattern to that seen in the Edinburgh Vein Study.

If the prevalence of varicose veins was truly higher in men than women in the Edinburgh Vein Study population, it may be that changes in lifestyle, working practices or the environment have led to a change in the sex differences since the first studies on varicose veins were performed in the 1960's and 1970's. However, the evidence to support any association between varices and lifestyle factors such as prolonged standing, tight undergarments, toilet posture, chair sitting and dietary fibre intake is lacking (Callam 1994).

As discussed in Chapter 2, few other studies have specifically investigated the prevalence of skin changes of CVI. The few studies which have done so (Table 2.4) exhibit no consistent pattern in the prevalence of CVI by sex.

7.3.3 Association with body mass index and weight

There is controversy in existing studies over the relationship between obesity and venous disease. Some authors have found a relationship between weight or BMI and

varicose veins. Abramson et al. (1981) found a positive association between weight and varicose veins in men aged 20-40 years and in women of all ages. After adjusting for age, Beaglehole et al. (1975) found a positive relationship between BMI and varicose veins in the subgroup of Maori males only, in his study of South Pacific islanders. In a study of Paris policemen, Ducimetiere et al. (1981) found there was an increasing mean BMI with increasing severity of varicose veins (groups adjusted for police rank, but not for age). In European women cotton workers, Mekky et al. (1969) found a significant increase in the prevalence of varicose veins with increasing weight, although no adjustment was made for age. When BMI was examined, only the 15-34 year old age group showed a positive association between BMI and prevalence of varices. When a group of men and women from Finland were analysed according to BMI quintiles, the lowest quintile had the lowest age-adjusted prevalence of varicose veins reported in a questionnaire. However, the remaining quintiles did not show any pattern in the prevalence of varices (Sisto et al. 1995).

Stvrtinova et al. (1991) found increasing prevalence of varicose veins with increasing BMI in a group of women working in a department store, but the results were not adjusted for age. Franks et al. (1992) found that although patients with venous disease were taller and heavier than those without, there was no significant difference in BMI. Once again there was no account taken of the age differences between the two groups. The importance of adjusting for age is illustrated in a study of women working in a department store. The relationship between increasing prevalence of varicose veins and increasing weight in these women disappeared when the results were adjusted for age (Guberan et al. 1973).

Other authors have found no relationship between varicose veins and weight or obesity (Hirai et al. 1990, Komsuoglu et al. 1994, Malhotra 1972, Stanhope 1975). Finally, some studies have found a positive relationship between obesity and varicose veins in women but not men. Canonico et al. (1998) found a significant association between BMI and weight and varicose veins in women but not men from South Italy aged over 65 years. In the Framingham Study, the age-adjusted incidence of varicose veins was significantly higher among women who were obese ($>27\text{kg/m}^2$) than those who were not. Although the incidence was also higher in obese men, the difference did not reach statistical significance (Brand et al. 1988).

In the Edinburgh Vein Study, there was an apparent increase in the prevalence of trunk varicose veins in women, and an increase in the prevalence of CVI in both sexes, across increasing quartiles of BMI. However, when the prevalence in each BMI quartile was adjusted for age, these trends disappeared. In men however, the resulting age-adjusted prevalence of trunk varicose veins decreased linearly across increasing BMI quartiles ($p \leq 0.001$). The age-adjusted prevalence of CVI in men was also highest in the lowest BMI quartile. One possible explanation for seeing this relationship in men but not in women, could be that less subcutaneous fat in thin men compared to thin women allows veins to be more easily seen in men, which might result in them being more often classified either as varicose veins or as a venous flare at the ankle (grade 1 CVI). Whatever the explanation, the hypothesis that varicose veins are associated with obesity is not supported by the results from the Edinburgh Vein Study.

7.3.4 Treatment for varicose veins

The prevalence of treatment for varicose veins in a population may be affected by factors such as treatment availability and perceived severity of the condition by the patient, in addition to the clinical severity of the varices. In a population survey in West London, 7% of subjects questioned said that they had used support stockings for a venous complaint (Franks et al. 1992) while 4.3% of patients attending a health centre in Brazil who had varicose veins had been operated on for the condition (Maffei et al. 1986). Results on the prevalence of treatment for varicose veins in men and women obtained in other studies are shown in Table 7.2. Despite differences in methods and study populations, a common finding was that treatment for varicose veins was more prevalent in women than in men. This was also true for the Edinburgh Vein Study population, despite the fact that trunk varices were more commonly found in men in this study population. This presumably partly reflects the increased cosmetic importance attributed by women to varicose veins compared to men, whose legs are more often covered by clothing.

7.3.5 Methodological bias

In the Edinburgh Vein Study, the question which arises therefore is whether the prevalence of trunk varicose veins and CVI in men was really higher than in women, or whether this result was due to bias. Differential measurement error was unlikely because the method used to identify venous disease was based on a standardised classification (Widmer 1978), and classification of trunk varicose veins and CVI showed 'fair to good' agreement with a second objective classification based on

colour photographs (Fleiss 1981). Furthermore, the two principal observers classified almost identical proportions of men and women as having trunk varices and CVI. In addition, venous incompetence measured by duplex scanning was significantly more common in the deep veins in men than in women. Alternatively, the results may have been biased if men with varices were more likely to attend than women with varices. However, comparison of the prevalence of doctor diagnosed varices between male and female non-responders and attenders suggests that this was unlikely (Figure 5.3). In conclusion, there is no evidence to suggest that a bias led to the higher prevalence of varicose veins and CVI in men observed in the Edinburgh Vein Study, although such bias cannot be ruled out in studies such as this.

7.3.6 Information on non-responders

The usefulness of the information obtained on the non-responders is dependent on how representative this group was of all the study non-responders. Those non-responders who returned their questionnaires were not significantly different with regard to age or sex from those who did not return their questionnaires, but came from relatively more affluent postcode sectors. Similarly, the non-responders from practices 1-4 (the practices selected for the non-response follow-up study) had no significant age or sex differences compared to the non-responders from practices 5-12, but had more affluent Carstairs deprivation scores. Among the study attenders, there was no significant difference in the median 'depscores' between those with trunk varices and those without varices. Therefore, the fact that the non-responders

on whom information of venous status was available had relatively more affluent Carstairs scores than those for whom no information on venous status was available, was not considered to adversely affect the ability of this group to represent the study non-responders as a whole.

Answers in the non-responders' follow-up questionnaire indicated that they were less likely than study attenders to have a previous doctor's diagnosis of varicose veins (age-adjusted prevalence 6.5% in non-responders versus 13.3% in attenders). However, when analysed by sex, this difference in prevalence between non-responders and attenders was significant only for women. Those non-responders who were asked on the telephone whether they had varicose veins were only a subset of the total group who declined to attend the Edinburgh Vein Study, and may have differed in some way from the whole. In addition, this method relied on self-reporting of varicose veins which may be inaccurate and subject to bias. Accepting these reservations, 11% of those questioned on the telephone reported having varicose veins. Once again, the perceived prevalence of varicose veins was significantly higher in women compared to men among this subset of non-responders. Furthermore, this figure was comparable to the 13.8% of non-responders who said on their questionnaires that they themselves thought they had varicose veins.

The information on previous doctor's diagnosis from the non-responders questionnaires was used to estimate the proportion who would have had varicose veins on examination had they attended. This was calculated assuming that the same

relationship would exist in the non-responders between a reported doctor's diagnosis of varicose veins and varices on examination, as in the study attenders. The resulting estimate proposed that around one third of men and one quarter of women in the general population have trunk varicose veins. This calculation involved many assumptions but is the best estimate available, taking into account the effect of the estimated non-response bias.

7.4 VENOUS REFLUX

7.4.1 General population perspective

Studies correlating reflux findings on duplex scanning with various stages of venous disease have increased knowledge of the patterns of reflux in venous patients (Weingarten et al. 1993, Labropoulos et al. 1994a, 1994b and 1996). In addition, the reflux patterns in apparently healthy volunteers have been described in two small studies (Labropoulos et al. 1995a and 1997). In the Bochum Study, the venous Doppler and clinical findings on the lower limbs of a cohort of German schoolchildren were reported (Schultz-Ehrenberg et al. 1992). However, to our knowledge, no previous study has investigated the distribution of venous reflux on duplex scanning in a large random sample of the adult population. The Edinburgh Vein Study provides new information on the prevalence of venous reflux in the general population and further examines the relationship between venous reflux at different anatomical sites and the clinical manifestations of venous insufficiency. These issues will be considered in turn.

7.4.2 Prevalence of reflux in individual vein segments

Overall, the prevalence of reflux was very similar in the right and left legs (Table 6.1). Generally, if the right leg segment had reflux, the likelihood that the same segment in the left leg would also have reflux was 20-35%, rising to more than 40% in the LSV segments. The choice of cut-off point for significant reflux made little difference to results in the superficial vein segments, since in most cases reflux of at least 0.5 seconds duration was in fact greater than 1 second duration. This was not the case in the deep veins however, and although 9-12% of subjects had reflux in the popliteal vein segments of ≥ 0.5 seconds duration, only 4-5% showed reflux greater than 1 second duration.

7.4.3 Prevalence of reflux by sex

A higher prevalence of reflux in men compared to women was found in the deep vein segments (Figure 6.1). However this difference only reached statistical significance in two of the five deep vein segments for $RD > 1.0$, compared to four of the five for $RD \geq 0.5$. This suggests that it may be appropriate to use different cut-off points for duration to define significant reflux in the deep veins in men and women. This might be the case if, for example, men were generally found to have larger veins which could accommodate more forward and reverse flow than women. However, in subjects with 'no disease', the median for duration of reflux in the deep vein segments were only 0.02 to 0.05 seconds greater in men compared to women. In addition, the higher prevalence of reflux in men did correspond with the higher prevalence of varicose veins and CVI in men compared to women in this study.

Conversely, a higher proportion of women than men had reflux in the superficial vein segments, although these sex differences failed to reach statistical significance.

The sex differences in the prevalence of reflux have not been previously reported in a general population sample. However the overall sex picture in the Edinburgh Vein Study was similar to that found in the Bochum Study, which examined German schoolchildren on three occasions during their education, at age 10-12, 14-16 and 18-20 years (Schultz-Ehrenberg et al. 1992). By the third examination, males had a higher prevalence of trunk varices, branch varices and incompetent perforators than females, but females had a higher prevalence of reflux in the saphenous veins on Doppler examination. In addition, there was an increase in the prevalence of reflux with increasing age of the children at successive examinations, particularly in the external iliac and the saphenous veins. In general, there was also a higher prevalence of reflux in the older age groups in the Edinburgh Vein Study.

7.4.4 Patterns of reflux

When the patterns of reflux were examined, the proportion of subjects with $RD \geq 0.5$ in the CFV segments in both legs greatly exceeded the proportion who also had reflux in the LSV and/or SFV segments (Table 6.2(a)). However for $RD > 1.0$, there was less of a discrepancy. The CFV segment was the one segment in which turbulent flow was often recorded and it may be that the size of this vein means it can accommodate forward and reverse flow to a greater extent than any of the other segments examined, without necessarily having an incompetent distal valve.

Similarly, the proportion of subjects with reflux in the above knee popliteal segments exceeded the proportion who also had reflux in the below knee popliteal and/or SSV segments (Table 6.2(b)). Possible explanations for this include the presence of reflux down incompetent gastrocnemial veins or unusual venous drainage in the popliteal area (Labropoulos et al. 1994a, Somjen et al. 1992). The latter possibly contributed to the relatively high number of missing results for the SSV segments in the Edinburgh Vein Study. If the SSV segment could not be confidently identified as such, it was recorded as missing rather than risk misclassification.

7.4.5 Cut-off point for significant reflux

While duplex scanning has become the method of choice for investigation of venous reflux (Porter et al. 1995, Labropoulos 1996), controversy over the method still exists. Different patient positions and techniques to elicit reflux have been evaluated in various studies (Welch et al. 1996) but techniques still vary. There is also debate over what constitutes significant reflux (Lagattolla and Burnand 1995). While some authors use duration of reverse flow of greater than 0.5 seconds as a definition for significant reflux (Araki et al. 1993, Bays et al. 1994, Masuda et al. 1994, Neglen and Raju 1993, Sakurai et al. 1997, Welch et al. 1996), others argue that this definition would include individuals with normally functioning veins (Lagattolla and Burnand 1995), and use a value of greater than 1 second duration (Labropoulos 1995b, Somjen 1992).

Results from the Edinburgh Vein Study have been presented comparing duration ≥ 0.5 seconds and > 1.0 second as a cut-off point to define significant reflux. Determining which cut-off point to use is not a straightforward issue. Using $RD \geq 0.5$ decreases the specificity, and risks defining more normal veins as incompetent, while using $RD > 1.0$ decreases the sensitivity, and risks defining more incompetent veins as normal. In this study, there was considerable overlap in duration of reflux in individual vein segments between those with and without 'venous disease'; 35% of 'disease-free' subjects had $RD \geq 0.5$ and 18% $RD > 1.0$ in at least one vein segment. There are obvious limitations in using presence of reflux in individual vein segments as a test for the presence or absence of 'venous disease'. Accepting these limitations, calculations of sensitivity and specificity showed little difference between using $RD \geq 0.5$ or $RD > 1.0$ as the cut-off point for duration of reflux in the in the upper LSV segment, as a test for venous disease (Figure 6.4(a)). However, in the below knee popliteal vein segment, sensitivity and specificity calculations tended to favour the use of 0.5 seconds as the cut-off point (Figure 6.4(b)).

7.4.6 Association between reflux and venous disease

There was a higher prevalence of reflux at all vein segments measured in those with 'venous disease' compared to those with 'no disease'. However, as previously mentioned, the duration of reflux in individual vein segments between these two groups of subjects showed considerable overlap (Table 6.3). For example, approximately 12% of those with 'no disease' had reflux ≥ 0.5 seconds duration in the popliteal and lower thigh LSV segments (Figure 6.3). When $RD > 1.0$ was used, these

figures dropped to 3-4% for the popliteal vein segments but remained at 10.7% for the lower thigh LSV segment. Long term follow-up is required to determine if this reflux reflects a preclinical stage prior to the development of varices (Schultze-Ehrenberg et al. 1992) and CVI in these subjects.

In a study which scanned upper and lower leg veins, Labropoulos et al. (1995a) found reflux >1 second duration in the superficial veins of 45% of limbs in symptom-free vascular surgeons and 26% of limbs of an age- and sex-matched control group without a history of venous disease. The most common site for superficial reflux was the below-knee segment of the LSV, demonstrating reflux in 29% (16/56) of vascular surgeons' limbs and 10% (8/50) of control group limbs. In another study involving duplex scanning of the whole leg, the same group of researchers found reflux >0.5 seconds duration in 14% of limbs (11/80) of subjects with no symptoms and 77% of limbs (31/40) of subjects with prominent but non-varicose veins who were referred for cosmetic reasons or due to mild symptoms (Labropoulos et al. 1997). In the Edinburgh Vein Study, 35% of subjects with 'no disease' had $RD \geq 0.5$ in at least one vein segment.

In the Edinburgh Vein Study, the prevalence of reflux at each vein segment increased with increasing severity of trunk varicose veins for both men and women, and the prevalence of reflux was significantly higher in subjects with CVI than in those without. These findings are generally in agreement with results from other studies. For example, Myers et al. (1995) found that, compared with limbs with uncomplicated varicose veins, superficial reflux occurred more frequently in limbs

with ulceration ($p < 0.05$) and deep reflux occurred more frequently in all limbs with complications ($p < 0.01$). In another study, Labropoulos et al. (1996) found that the extent and distribution of reflux correlated with severity of CVI, in subjects ranging from asymptomatic (Class 0 CVI) through to moderate CVI (Class 2 - skin changes of hyperpigmentation, brawny oedema and subcutaneous fibrosis and local/regional dilatation of subcutaneous veins, (Porter et al. 1988)). LSV incompetence was more common than SSV incompetence and the deep veins most commonly affected by reflux were the calf veins followed by the popliteal veins. This corresponds with the Edinburgh Vein Study, where the LSV and popliteal veins most often showed reflux (calf veins were not scanned).

In the Edinburgh Vein Study, the tendency for men to have a higher prevalence of reflux in the deep vein segments and women in the superficial vein segments was generally maintained across severity of varices. It is not clear why the prevalence of grade 1 trunk varices in men was significantly higher than in women (Table 5.1), while the prevalence of reflux was higher in the superficial veins of women with grade 1 trunk varices compared to men with grade 1 trunk varices (Table 6.4). It is possible that, for some reason, a different pattern of incompetence develops in men and women, leading women to develop reflux in the main saphenous trunks, while men develop reflux and varices in the branches of the saphenous trunks. The higher prevalence of grade 1 trunk varices in men could then be explained by varices of branch veins in the calf or thigh (which were not scanned in our study), while the main saphenous trunks (which were scanned) remained competent. However, this is a hypothesis for investigation in a future study.

7.5 PUBLIC HEALTH IMPLICATIONS OF VENOUS DISEASE

7.5.1 Health service utilisation

It has been shown in the Edinburgh Vein Study that varicose veins and CVI are very common conditions which increase with age. A substantial proportion of the study participants, more often women, had received treatment for the condition. Of the approximately 7000 varicose vein operations performed in Scotland during 1997, more than two thirds were on women (ISD, NHSiS, unpublished data). These figures reflect the substantial cost of venous conditions to the National Health Service. However, they can only represent the tip of the iceberg, if one third of the general population has some degree of varicose veins as suggested by the Edinburgh Vein Study.

Conversely, varicose veins do not represent a large workload for General Practitioners (GPs). In a representative sample of Scottish General Practices, the consultation rate for varicose veins during 1997 was 510 per 100,000 population for men and 889 per 100,000 population for women. The rates for leg ulcers were 138 and 279 per 100,000 for men and women respectively (J.W.T. Chalmers, personal communication). Extrapolating from these data, a GP with an average practice size of 1500 patients (J.W.T. Chalmers, personal communication) might expect to see 11 patients with varicose veins and 3 patients with leg ulcers per year. Similarly, from the Edinburgh Vein Study population, approximately 13 people would be expected to consult their GP about varicose veins and 2 about leg ulcers during course of a year. The relatively small number of consultations for varicose veins may be partly

because patients can often be dealt at the first visit to the GP either by referral for surgery or reassurance. Consultation rates will also be affected by patient perception of severity of the condition; some may not consider varicose veins as a problem worthy of consulting their doctor. In the Edinburgh Vein Study attenders, 9.7% of men and 17.5% of women reported that they had a previous doctor's diagnosis of varicose veins, indicating that they had consulted a doctor about the condition. These figures were low, especially for men, when compared to the prevalence of trunk varices found on examination (men 39.7%, women 32.2%).

Leg ulcers are a chronic condition, yet also appear to lead to few GP consultations. This is presumably because in the UK, ulcers are usually managed by district nurses rather than GPs. In 1992, it was estimated that approximately 30% of district nursing time was spent dealing with leg ulcer patients, making this service the largest component of the cost of treating venous disease in Britain (Laing 1992). However, due to recent changes in bandages and dressing techniques, this figure is now reportedly falling (F.G.R. Fowkes, personal communication).

7.5.2 Health service provision

Health service utilisation is influenced by provision of services. Public expectations and patterns of referral and admission may all be affected by ease of access to treatment (Robbins et al. 1994). In the past, surgery for varicose veins has been rationed to some extent by long waiting lists. Waiting times have been as long as five years, but are now generally required not to exceed 18 months (Corbett 1999).

No apparent association between deprivation and prevalence of varicose veins was found in the Edinburgh Vein Study. However inequalities in health care may well arise from the implicit rationing discussed above, since those who can afford it may seek treatment elsewhere. It was estimated that around 25% of varicose vein operations in England and Wales in 1990 were performed in the private sector (Robbins et al. 1994). Reliable data on private operations in Scotland is not currently available (J.W.T. Chalmers, personal communication).

Restrictions on varicose vein surgery in the NHS are now becoming more explicit. In Scotland in 1999, two of the 15 health boards had restrictions on varicose vein surgery for cosmetic reasons and a third demanded appropriate clinical indications for surgery (Directors of Public Health, personal communications). Therefore, rationing of varicose vein treatment is already taking place in some parts of Scotland, on a geographical basis. The Edinburgh Vein Study has shown that around one third of the population aged 18-64 years has some degree of varicose veins. Not all of these people will need or desire surgery for their condition. However, treatment for an appropriate level of disease needs to be available on an equitable basis throughout the country.

7.5.3 Evidence-based planning

Information required

Health authorities need to determine the level of treatment which should be provided in order to give patients maximum benefit. In order to do this, information is required on:

- the prevalence in the population of the condition for whom treatment is indicated and desired.
- the effectiveness of treatment.
- the cost-effectiveness of treatment in relation to other services.

For varicose veins, evidence in all of these areas is lacking (Robbins et al 1994).

Prevalence and natural history

Information on the prevalence and severity of venous disease is required from studies of the general population in order to identify the potential need for treatment. The natural history and progression of venous disease needs to be ascertained before it is possible to identify which patients will benefit most from treatment. Varicose veins are relatively common but only around 1% of the population will develop a leg ulcer in their lifetime (Callam 1992). At present, there is no clear way of predicting which limbs with varicose veins are at risk of progressing to ulceration (London and Nash 2000).

The cross-sectional phase of the Edinburgh Vein Study provides up to date and detailed information on the prevalence and severity of varicose veins and CVI on a random population sample. The planned follow-up of the study cohort will provide important information on the natural history and progression of venous disease. It will also determine the extent to which venous reflux on duplex scanning can predict future occurrence of venous disease and of complications in those who already have disease.

Effectiveness of treatment

The effectiveness of the different types of treatment for varicose veins remains unclear (Robbins et al. 1994). An important question is whether progression from varicose veins to ulceration can be prevented by surgical treatment (Corbett 1999). Operating on varicose veins early has not been shown to reduce the socio-economic burden of venous ulceration. Long term epidemiological and clinical studies are required to demonstrate the benefits or otherwise of surgery (Bradbury et al. 1999). There is little evidence to show that removing varicose veins ameliorates lower leg symptoms (Baker et al. 1995). Furthermore the association between leg symptoms and signs of varicose veins in the Edinburgh Vein Study was found to be poor (Bradbury et al. 1999). Patient satisfaction following treatment is another area requiring further investigation (Robbins et al. 1994).

Cost-effectiveness of treatment

There has been little economic evaluation of treatment for varicose veins (Robbins et al. 1994). Much more information is required on the costs and benefits of different therapies and modes of healthcare delivery for venous diseases. This will help identify a valid point at which management of venous disease should be initiated, and whether a move from demand-led to more proactive management is justified (Laing 1992). The scope for preventive measures is unclear as evidence on the effect of most lifestyle factors on venous disease is inconclusive (Kurz et al. 1999). The Edinburgh Vein Study has shown that a large proportion of the population have varicose veins. Current information cannot identify for which of those people treatment is cost-effective, nor determine the ideal level of treatment. Cost-effectiveness data is also required to determine where treatment for varicose veins should lie on the NHS list of priorities (Robbins et al. 1994).

7.5.4 The future

The follow-up of the Edinburgh Vein Study population will provide important information on venous disease progression and detection. Other longitudinal studies of venous disease are also underway (Cesarone et al. 1997). An international task force on venous disease has called for randomised clinical trials of therapies for venous disease with long term follow up, and studies into the cost-effectiveness of early intervention for venous ulcer prevention (Kurz et al. 1999). In the meantime, as life expectancy increases and the proportion of elderly people grows, the prevalence of venous conditions at the more severe end of the spectrum will also increase

(Bosanquet 1992). Pressure on NHS funding continues and health authorities will be increasingly forced into making decisions on the rationing of treatments, based on inadequate evidence.

Table 7.1 Prevalence of varicose veins in males and females from surveys of the general population

First Author	Year	Location	Age (Years)	Method	Definition	Male %	Female %
Coon	1973	Tecumseh USA	> 10	Examination	Prominent superficial veins in the lower extremities	12.9	25.9
Abramson	1981	Jerusalem Israel	> 15	Examination	Distended and tortuous subcutaneous veins, excluding very small veins (venectasias)	10.4	29.5
Franks	1992	London England	35-70	Questionnaire	Asked "Have you ever had large veins or varicose veins in your legs?"	^a 17	^a 31
Sisto	1995	Finland	>30	Questionnaire	Asked whether a physician had ever made a diagnosis of varicose veins	6.8	24.6
^b EVS		Edinburgh Scotland	18-64	Examination	Dilated, tortuous trunks of the long or short saphenous veins and their branches of 1st or 2nd order	39.7	32.2

Footnote:

- ^a Calculated from original report (Franks et al. 1992). Figures are approximate due to unspecified missing values.
- ^b Results from the Edinburgh Vein Study

Table 7.2 Prevalence of treatment for varicose veins from different surveys

First Author (Year)	Subjects	Treatment	% Male	% Female
Widmer (1978)	All subjects	Stripping/sclerotherapy	7	19
		Compression	3	8
Abramson (1981)	Subjects with varices	Any treatment	15	32
Laurikka (1993)	All subjects	Any treatment	5	17
	Subjects with varices		25	41
Sisto (1995)	All subjects	Surgical operations	1.9	13.2
	Subjects with varices		29	53
Canonico (1998)	Subjects with varices	Surgery	1.1	3.1
		Sclerotherapy	0	3.1
		Other	21.8	37.7
		Stockings	7.4	20.2
EVS (Results from Edinburgh Vein Study)	All subjects	Operation	5.1	7.8
		Injection	1.4	5.7
		Compression	2.9	9.0

CHAPTER 8

CONCLUSIONS AND

RECOMMENDATIONS FOR FUTURE RESEARCH

8.1 CONCLUSIONS

The following conclusions can be drawn from the Edinburgh Vein Study:-

1. Venous disease is common in the general population. Trunk varicose veins affect around one third of the adult population while mild reticular and hyphenweb varices are 'the norm'.
2. Mild trunk varices and CVI are at least as common in men as in women.
3. The prevalence of clinical signs of venous disease does not differ significantly between the right and left legs.
4. The prevalence of venous disease increases with age.
5. The prevalence of trunk varices and CVI are not significantly related to social class.
6. There is no clear relationship between trunk varicose veins or CVI and body mass index, once age has been taken into account.
7. Women are more likely to have treatment for varicose veins than men.
8. The prevalence of venous reflux in individual vein segments on duplex scanning does not differ significantly between the right and left legs.

9. Of the vein segments from the groin to behind the knee, the lower thigh long saphenous vein segment is most often affected by reflux. Of the deep vein segments, the above knee popliteal segment is most often affected.
10. Venous reflux in the deep vein segments is more common in men than women. There is a tendency towards a higher prevalence of reflux in the superficial segments in women, although in this study, the sex differences in the superficial veins did not reach statistical significance.
11. There is a general trend towards a higher prevalence of reflux in the older age groups in many vein segments.
12. There is a positive association between the prevalence of reflux in individual vein segments and the presence and severity of venous disease.
13. There is considerable overlap in duration of reflux in individual vein segments between those with and without 'venous disease'.
14. The cut-off point at which reflux duration becomes clinically significant is not clear-cut.
15. In this study, there was little difference between the proportion of subjects with reflux ≥ 0.5 seconds and > 1.0 second in the superficial vein segments. However, in the deep vein segments, the prevalence of reflux ≥ 0.5 seconds was 2 to 4 times higher than the prevalence of reflux > 1.0 second.
16. Calculations of the sensitivity and specificity of the duration of reflux in the below knee popliteal segment as a measure of venous disease tended to favour $RD \geq 0.5$ over $RD > 1.0$ as a cut-off point.

17. Recruiting working-age subjects from the general population to participate in a study to investigate venous disease is problematic. It is important to consider the impact which non-responders may have on the results of such a study.

8.2 RECOMMENDATIONS FOR FUTURE RESEARCH

1. Future studies should use a standard classification for chronic venous disease, such as the CEAP classification. This will help when comparing results with other studies.
2. Future studies should use methods of measurement of venous function such as duplex scanning and phlethysmography in addition to clinical examination, in order to increase the objectivity of measurement of venous disease.
3. The scientific literature does not indicate the extent to which venous disease is an inherited or an acquired condition. Family and genetic studies are needed to answer this question.
4. Further investigation is required to clarify the risk factors for venous disease. Identification of modifiable risk factors would open up possibilities for prevention of this common disease.
5. Further work is required to relate patterns of reflux to clinical disease. This will help to clarify the significance of venous reflux in individual vein segments.
6. Longitudinal studies are required to determine the extent to which venous reflux is a predictor of venous disease development or progression. A marker of future complications would help to identify those people most likely to benefit from early intervention.

7. Long term follow-up studies are required to determine incidence, natural history and progression of venous disease, in study samples representative of the general population. This should identify those people in whom disease is most likely to progress and indicate who to target with early intervention.
8. Randomised clinical trials of varicose vein treatment with follow-up of patients are required. This will help to identify which interventions are effective in preventing disease progression in the long term.
9. Further work is required on patient satisfaction following varicose vein treatment. Correlation between symptoms with signs of venous disease has been shown to be poor (Bradbury et al. 1999). Methods are required to help surgeons determine which patients will gain relief from their symptoms on receiving treatment for their veins.
10. Research should be conducted on the cost-effectiveness of varicose vein treatments. The condition is at least as common in men as women, but at present, more women than men receive treatment for varicose veins. Evidence on cost-effectiveness is required to aid decisions on the level of provision and prioritisation of varicose vein treatments in the NHS.

It is hoped that the planned long term follow-up of the Edinburgh Vein Study population will provide an opportunity to answer some of these research questions.

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APPENDICES

INVITATION LETTER TO SUBJECTS



Ref. No. 1~

23 December 1996

2~ 4~ 3~,
5~,
6~, 7~.

Dear 2~ 3~,

EDINBURGH VEIN STUDY

Wolfson Unit for the Prevention of
Peripheral Vascular Diseases
The University of Edinburgh
Teviot Place
Edinburgh EH8 9AG
Fax 0131 650 6904
Telephone 0131 650 4555

EDINBURGH VEIN STUDY

You may know that varicose veins and leg ulcers are very common conditions. The University of Edinburgh, in collaboration with your general practice, is conducting a study to find out more about the causes and prevention of these diseases and we are writing to request your help with the research. We are working with consultants from the Royal Infirmary of Edinburgh and about 1500 people will be taking part, including many with perfectly normal legs as well as those with varicose veins.

We hope that you will take part in the project. You will be invited to attend a clinic at the University of Edinburgh on one occasion only for the examination of your legs, during which refreshments will be served. The whole appointment should take just over one hour. We will also send you a questionnaire to fill in before you come.

Please fill in the attached form to indicate when you are able to attend. Travelling expenses will be reimbursed at the clinic (Teviot Place). If you have difficulty in getting off work, we will be pleased to contact your employer. If you have problems getting to the clinic due to illness or disability, we would be pleased to visit you in your own home.

We hope that you will be able to help with this research. It is very important that nearly everyone who is approached takes part. You will be helping us to find out more about diseases which cause a lot of discomfort to many people in Scotland.

If you have any queries, please do not hesitate to contact Christine Evans (tel. 650- 4555).

Yours sincerely,

Dr. Christine Evans
University of Edinburgh

8~
Muirhouse Medical Group

MEDICAL INVESTIGATORS

F G R Fowkes C J Evans P L Allan J M Connor G D O Lowe C V Ruckley

INVITATION LETTER TO SUBJECTS

Reference :- 1 ~

Please fill in and return this slip in the prepaid envelope and we will send you more details of the study and your involvement.

Title (Please delete as appropriate) :-

Mr / Mrs / Miss / Ms / Dr / Rev other

Name :- 4 ~ 3 ~

Address :- 5 ~, 6 ~ 7 ~

Telephone No :- Home: 9 ~ Work:

1. I am willing to participate in the research study. Please send me further details and an appointment for the examination of my legs.

Please tick all the options which apply:-

I am able to attend in the morning (9am-12noon)

I am able to attend in the afternoon (12noon-5pm)

I cannot attend on the following days
.....

I am unable to attend at the above times, but could come to an evening clinic (5-8pm)

I cannot attend on the following evenings
.....

I am unable to attend the clinic but would like a home visit

2. I am unable to take part in the study

APPOINTMENT INFORMATION



Ref. No. 1~

23 December 1996

2~ 4~ 3~,

5~,

6~, 7~.

Dear 2~ 3~,

EDINBURGH VEIN STUDY

Wolfson Unit for the Prevention of
Peripheral Vascular Diseases
The University of Edinburgh
Teviot Place
Edinburgh EH8 9AG

Fax 0131 650 6904

Telephone 0131 650 4555

EDINBURGH VEIN STUDY

Thank you for volunteering to participate in this study. We should be grateful if you would attend the clinic at the University Medical School at :

Day :- 10~ 8~

Time :- 9~

If this appointment is not suitable, please let us know as soon as possible and we will arrange an alternative one. This can be done by telephoning 031-650-4555 in the morning between the hours of 9am -12.30pm or by leaving a message outwith these hours.

Enclosed with this letter are the following :-

1. The Questionnaire

Would you please fill in this questionnaire before your appointment and bring it to the clinic with you. If you have any difficulty with the questions, there will be a chance to discuss them with the staff at the clinic.

2. Subject Information Sheet

This gives you information about the study and details of what is involved when you attend for your appointment at the clinic.

3. Map

This describes where the clinic is situated and the bus routes.

Preparation for the examination.

* If you wear spectacles for reading, please bring them with you.

* The ultrasound scan involves an examination from the top of your legs down to the knees. Please note that any tight underwear worn (eg. corsets) will have to be removed for this examination.

If you have any queries, please do not hesitate to 'phone Christine Evans on 650-4555. We are very grateful for your co-operation.

Yours sincerely,

Dr. Christine Evans
Clinical Research Fellow

MEDICAL INVESTIGATORS

F G R Fowkes C J Evans P L Allan J M Connor G D O Lowe C V Ruckley

APPOINTMENT INFORMATION

EDINBURGH VEIN STUDY - SUBJECT INFORMATION SHEET

Aims of the study

The purpose of this study is to find out the extent to which diseases of the leg veins are present in Edinburgh people. It will also help identify what factors might cause varicose veins. The results of the study may hopefully lead to the development of measures to prevent this condition in the future.

Participants

We are examining around 1500 people, aged between 18 and 64 years and registered with general practices in the city of Edinburgh. People are selected at random and may or may not have had previous problems with their leg veins.

The Medical Examination

You will be asked to fill in a questionnaire about your past medical history, previous occupations, diet etc. There will be an opportunity to discuss this with the staff at your appointment at the clinic.

At your appointment you will have an ultrasound scan of your legs so that we can see the blood flowing in your veins. This scan is quite painless and is of the type used to scan pregnant women. You will be required to stand on a tilting couch, have a small amount of jelly put on your legs and will then be scanned with the ultrasound detector. Your calf and thigh muscles will be squeezed gently to see in which direction the blood is flowing.

We will examine your legs and take three colour photographs of them to look for any varicose veins. You will also have your height and weight measured. Finally we will take a small blood sample from your arm to test for various factors thought to be important in the development of diseases of the veins. Altogether these procedures should take around one and a quarter hours. We will give you a form to take away with you to make a record of your next three bowel movements. You will be asked to post this form back to us.

There are no foreseeable risks in taking part in this study. You will have to stay reasonably still for about half an hour during the scan but you will be free to move around at any time you feel the need. A small amount of discomfort is sometimes felt on having a blood sample taken. Refreshments will be served during your visit. Following the initial study we may wish to review your condition, at some stage in the future.

General Information

You are in no way obliged to take part in this study and you are also free to withdraw at any time. Such decisions will not affect any treatment you might normally receive from your doctor.

Your general practitioner will be informed of your decision to take part and of any clinically significant results.

Travel expenses will be refunded as required.

Should you want any further information, please do not hesitate to contact:

Dr. Christine Evans,
Wolfson Unit, University of Edinburgh, Teviot Place,
Edinburgh EH8 9AG. Tel 0131-650-4555

Independent information about the study can be obtained from :

Dr. E. Housley (Consultant Physician),
Royal Infirmary of Edinburgh,
Lauriston Place, Edinburgh. Tel 0131-229-2477

STUDY QUESTIONNAIRE

EDINBURGH VEIN STUDY

QUESTIONNAIRE

The information you give in this personal health record will be treated as strictly confidential.
The results of the research will appear only in the form of general statistics.

Please complete the following:

SURNAME:

FORENAMES:

DATE:

--	--	--	--	--	--	--

Please bring this questionnaire along with you to your appointment.

If you have difficulty in answering any of the questions you will have a chance to discuss these later with a member of the study team.

THANK YOU FOR YOUR CO-OPERATION IN THIS STUDY.

STUDY QUESTIONNAIRE

PERSONAL HISTORY

1. Please tick one box Male Female
2. What is your date of birth? Day Month Year
- | | | | | | |
|--|--|--|--|--|--|
| | | | | | |
|--|--|--|--|--|--|
3. What is your marital status? (tick **one** box)
- | | |
|-----------------------|--------------------------|
| Married or equivalent | <input type="checkbox"/> |
| Single | <input type="checkbox"/> |
| Widowed | <input type="checkbox"/> |
| Divorced or separated | <input type="checkbox"/> |

EMPLOYMENT

4. What is your current employment situation? (tick **one** box)
- | | |
|--|--------------------------|
| Employed/Self-employed (full or part-time) | <input type="checkbox"/> |
| Unemployed | <input type="checkbox"/> |
| Housewife | <input type="checkbox"/> |
| Retired | <input type="checkbox"/> |
| Student or on a full-time training course | <input type="checkbox"/> |
5. Please complete the following for the occupation covering the longest period of the life of yourself and your most recent partner/spouse. If no recent partner/spouse, complete for your father.

Yourself	Partner/spouse <input type="checkbox"/> Father <input type="checkbox"/>												
Name of job	Name of job												
What does/did this job involve?	What does/did this job involve?												
What business or industry is/was this job in?	What business or industry is/was this job in?												
In this job are/were you:	In this job are/were they:												
<table style="width: 100%;"> <tr> <td>manager <input type="checkbox"/></td> <td>foreman/ supervisor <input type="checkbox"/></td> </tr> <tr> <td>self-employed <input type="checkbox"/></td> <td>employee <input type="checkbox"/></td> </tr> <tr> <td>apprentice/ trainee <input type="checkbox"/></td> <td></td> </tr> </table>	manager <input type="checkbox"/>	foreman/ supervisor <input type="checkbox"/>	self-employed <input type="checkbox"/>	employee <input type="checkbox"/>	apprentice/ trainee <input type="checkbox"/>		<table style="width: 100%;"> <tr> <td>manager <input type="checkbox"/></td> <td>foreman/ supervisor <input type="checkbox"/></td> </tr> <tr> <td>self-employed <input type="checkbox"/></td> <td>employee <input type="checkbox"/></td> </tr> <tr> <td>apprentice/ trainee <input type="checkbox"/></td> <td></td> </tr> </table>	manager <input type="checkbox"/>	foreman/ supervisor <input type="checkbox"/>	self-employed <input type="checkbox"/>	employee <input type="checkbox"/>	apprentice/ trainee <input type="checkbox"/>	
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self-employed <input type="checkbox"/>	employee <input type="checkbox"/>												
apprentice/ trainee <input type="checkbox"/>													

STUDY QUESTIONNAIRE

6. Think how you have spent most time during working hours throughout your life. You will be asked to mark lines with an X.

Example: a postman spends most of his working time walking and some of the time lifting heavy objects. He might mark the lines as follows:-

	All the time	Half the time	Never
Sitting	----- ----- -----X-----		
Standing	----- ----- -----X-----		
Walking	-----X----- ----- -----		
Heavy lifting	----- -----X----- -----		

Mark these lines for yourself to show how you have spent most time during working hours:-

	All the time	Half the time	Never
Sitting	----- ----- -----		
Standing	----- ----- -----		
Walking	----- ----- -----		
Heavy lifting	----- ----- -----		

EDUCATION

7. What is the highest level of education you have completed, or are currently undertaking?

Secondary school	
University or college degree course	
Other professional or technical qualification	

STUDY QUESTIONNAIRE

MEDICAL HISTORY

8. Have you ever been told by a doctor that you had any of the following?
(tick appropriate boxes)

	Right leg		Left leg	
	Yes	No	Yes	No
Varicose veins	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Leg ulcer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Phlebitis/vein inflammation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Swollen ankle or leg:-				
during or following pregnancy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
following operation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
other (specify.....)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Deep venous thrombosis (clot in the leg)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fractured/broken leg	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Yes	No		
Haemorrhoids (piles)	<input type="checkbox"/>	<input type="checkbox"/>		
Hernia (lump in the groin)	<input type="checkbox"/>	<input type="checkbox"/>		
Pulmonary embolism (clot on the lung)	<input type="checkbox"/>	<input type="checkbox"/>		
Marfan's syndrome	<input type="checkbox"/>	<input type="checkbox"/>		

9. Do you experience any of the following symptoms in your legs ?

	Right leg		Left leg	
	Yes	No	Yes	No
Heaviness and tension	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling of swelling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Aching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Restless legs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cramps	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Itching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tingling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

FAMILY HISTORY

10. Have any of these members of your family suffered from the following ?

	Varicose veins		Leg ulcer	
	Yes	No	Yes	No
Mother	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Father	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Brother/sister	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Grandparents	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other relatives (specify	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

STUDY QUESTIONNAIRE

VARICOSE VEINS

Women who have **not** had varicose veins - omit this section and go to question 15.
Men who have **not** had varicose veins - omit this section and go to question 19.

11. How old were you when you first developed varicose veins? years

12. Have you ever had compression treatment for your varicose veins (stockings or bandaging)?

	Right leg	Left leg
	Yes No	Yes No
	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>

13. Have you had the following treatments for varicose veins?

	Right leg	Left leg
	Yes No	Yes No
Operation	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
Injection of veins	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>

If you have **never** had an operation or injections for your varicose veins
 -women go to question 15.
 -men go to question 19.

14 a) Have your varicose veins come back since they were first treated? Yes No

If yes, how soon after treatment did they come back? Years Months

b) Have you had your varicose veins treated by operation or injection more than once? Yes No

c) In which hospitals have you had treatment for varicose veins?

Hospital	Year (approx.)

STUDY QUESTIONNAIRE

WOMEN ONLY

Men omit this section and go to Question 19.
--

15. a) What age did you start your periods? years
- b) Have you been through or started the menopause
(change of life/periods stopped)? Yes No
- If yes, at what age did the menopause start? years
16. a) Are you pregnant at the moment? Yes No
- b) How many times have you been pregnant ?
(include miscarriages and any current pregnancy) times
- c) Did any varicose veins first develop during pregnancy ? Yes No
- If yes, did any varicose veins disappear after pregnancy? Yes No
17. **Oral Contraceptive Pill.** Are you currently on the pill? Yes No
- If Yes, answer 17 a) If No, answer 17 b)
- a) **Yes** What is the name of the pill ?
.....
- How often do you take the pill ? 3 out of 4 weeks every day
- How many years in total have you been on
the pill ? (don't count any breaks) years
- b) **No** Have you ever been on the pill? Yes No
- If yes, how many years in total were you
on the pill ? (don't count any breaks) years
18. **Hormone Replacement Therapy.** Are you currently on HRT ? Yes No
- If Yes, answer 18 a) If No, answer 18 b)
- a) **Yes** What is the name of the tablets and/or patches ?
.....
- How many years in total have you been on HRT? years
- b) **No** Have you ever been on HRT ? Yes No
- If yes, how many years in total were you on HRT ? years

STUDY QUESTIONNAIRE

Both men and women, answer the following questions

DIET

Unless otherwise indicated, please ring the number of days per week you usually eat the following foods at this time of year.

e.g. Potatoes, boiled : If you eat these every day, answer like this :

(7) 6 5 4 3 2 1 F R

If you eat the food once every 2-3 weeks, ring F (=Fortnightly)

If you eat the food less than every 2-3 weeks or never, ring R (= Rarely)

Bread, Rice and Pasta

	No. days per week	No. slices per day	Thick/medium or thin slices	Large/medium or small loaf
19. White bread				
Brown/Hovis				
100% Wholemeal				

Rolls : Which type? No. eaten per week

- | | |
|----------------------------|-------------------|
| 20. <u>Brown</u> rice | 7 6 5 4 3 2 1 F R |
| 21. <u>Wholemeal</u> pasta | 7 6 5 4 3 2 1 F R |
| 22. Pasta (other) | 7 6 5 4 3 2 1 F R |

Vegetables

- | | |
|---|-------------------|
| 23. Potatoes : a) boiled / mashed | 7 6 5 4 3 2 1 F R |
| b) baked | 7 6 5 4 3 2 1 F R |
| c) chips / fried / roast | 7 6 5 4 3 2 1 F R |
| 24. Green beans / cabbage / sprouts | 7 6 5 4 3 2 1 F R |
| 25. Baked beans / butter beans | 7 6 5 4 3 2 1 F R |
| 26. Peas | 7 6 5 4 3 2 1 F R |
| 27. Carrots / parsnips / swede / cauliflower | 7 6 5 4 3 2 1 F R |
| 28. Salad vegetables (e.g. cucumber / lettuce / tomatoes) | 7 6 5 4 3 2 1 F R |
| 29. Other vegetables (please name) | 7 6 5 4 3 2 1 F R |

Biscuits, cakes and crisps

- | | |
|--|-------------------|
| 30. Digestive biscuits / rye crisp bread / bran biscuits | 7 6 5 4 3 2 1 F R |
| 31. Wheat crisp bread / oatcakes | 7 6 5 4 3 2 1 F R |
| 32. Other biscuits / cakes / buns | 7 6 5 4 3 2 1 F R |
| 33. Crisps (all varieties) | 7 6 5 4 3 2 1 F R |

STUDY QUESTIONNAIRE

Breakfast cereals

- | | |
|---|-------------------|
| 34. Rice Krispies / Special K / Sugar Puffs / Corn flakes | 7 6 5 4 3 2 1 F R |
| 35. Grapenuts / Ready Brek / Porridge | 7 6 5 4 3 2 1 F R |
| 36. Sultana Bran / Muesli | 7 6 5 4 3 2 1 F R |
| 37. 30% Bran Flakes / Puffed Wheat / Shreddies /
Spoon-sized Shredded Wheat / Cracklin' Bran | 7 6 5 4 3 2 1 F R |
| 38. Shredded Wheat / Weetabix | 7 6 5 4 3 2 1 F R |
| 39. All-Bran | 7 6 5 4 3 2 1 F R |
| 40. Wheat Bran | 7 6 5 4 3 2 1 F R |
| 41. Other cereal (please name) | 7 6 5 4 3 2 1 F R |

Fruit

- | | |
|--|--|
| 42. How many apples / pears do you eat per week? | <input type="text"/> |
| 43. How many oranges do you eat per week? | <input type="text"/> |
| 44. How many bananas do you eat per week? | <input type="text"/> |
| 45. Do you peel apples and pears before eating them? | Yes <input type="checkbox"/> No <input type="checkbox"/> |
| 46. Dried fruit (e.g. currants, dates, raisins,
sultanas, figs, prunes) | 7 6 5 4 3 2 1 F R |
| 47. Tinned fruit (all varieties) | 7 6 5 4 3 2 1 F R |
| 48. Nuts (e.g. brazils, hazelnuts, peanuts) | 7 6 5 4 3 2 1 F R |

BOWEL HABIT

49. How many days per week do you usually open your bowels? days per week
50. On the days that you open your bowels, how many times do you usually open them? times per day
51. How often do you strain severely, that is hold your breath and push down really hard, in order to start passing a motion?
 Only occasionally About half the time Nearly always
52. How often do you strain severely, that is hold your breath and push down really hard, in order to finish passing a motion?
 Only occasionally About half the time Nearly always
53. a) Do you regularly take laxatives other than bran? Yes No
- b) If yes, how often do you take them:-
 Nearly every day
 About 1-4 times a week
 Less than once a week

STUDY QUESTIONNAIRE

SMOKING

- 54 a) Do you smoke at present? Yes No

If No, go to part f)

- b) What do you usually smoke now?
- | | | |
|------------|--------------------------|--------------------------|
| | Yes | No |
| cigarettes | <input type="checkbox"/> | <input type="checkbox"/> |
| pipe | <input type="checkbox"/> | <input type="checkbox"/> |
| cigars | <input type="checkbox"/> | <input type="checkbox"/> |

If only pipes or cigars, go to part f)

- c) How many cigarettes do you usually smoke now? cigarettes per day
- d) For how many years of your life have you smoked cigarettes? years
- e) How many cigarettes have you smoked on average during the period you have smoked? cigarettes per day

Now go to part j)

- f) Have you ever smoked cigarettes regularly? Yes No

If No, go to part j)

- g) How many cigarettes did you smoke on average while you were a smoker? cigarettes per day
- h) For how many years did you smoke cigarettes? years
- i) How long is it since you gave up smoking cigarettes? years

Everyone answer part j)

- j) Are you exposed to cigarette smoke at home or at work? Yes No

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

REPORT TO GENERAL PRACTITIONERS



EDINBURGH VEIN STUDY

Wolfson Unit for the Prevention of
Peripheral Vascular Diseases
The University of Edinburgh
Teviot Place
Edinburgh EH8 9AG

Fax 0131 650 6904
Telephone 0131 650 4555

Ref. No :- 1~

23 December 1996

25~,
29~,
26~,
27~.

Dear 25~,

Re: 2~ 3~ 4~.
D. of B. 6~

The above patient was seen on 28~ as part of the Edinburgh Vein Study. I enclose copies of the consent form and Subject Information Sheet for your information. Also attached is a report of our findings on this patient. The leg examination consisted essentially of visual inspection of the legs. The Duplex scan demonstrates points of incompetence of the venous valves in the legs. Please bear in mind that this information is based on a classification for the purposes of research and is not intended to be a clinical diagnosis.

Patients inquiring about varicose veins were given an information leaflet produced by the Health Education Board for Scotland on "Help and Advice on Leg Problems - Varicose Veins", and advised to discuss the matter with their general practitioner if more information was desired.

We hope that this information may be of help.

Yours sincerely,

Dr. Christine J. Evans
Clinical Research Fellow

MEDICAL INVESTIGATORS

F G R Fowkes C J Evans P L Allan J M Connor G D O Lowe C V Ruckley

CONSENT FORM

Study Number.....

CONSENT FORM

Full title of study (a copy of the subject information sheet is attached):-

EDINBURGH VEIN STUDY - an epidemiological investigation into the aetiology of early venous disease

Further information is available from :-

Name of Investigator - Dr. Christine Evans
Address - Wolfson Unit for the Prevention of Peripheral Vascular Diseases, The University of Edinburgh, Teviot Place, Edinburgh EH8 9AG.
Telephone - 031-650-4555

Your General Practitioner will be informed of your participation in this study and will be advised of any clinically significant information that comes to light.

I agree to participate in this study.

I have read this Consent Form and the Subject Information Sheet and had the opportunity to ask questions about them.

I understand that I am under no obligation to take part in this study and a decision not to participate will not alter the treatment I would normally receive.

I understand that I have the right to withdraw from this study at any stage.

I understand that this is not research on treatment and that I cannot expect to derive any benefit.

Signature of Subject :-

Name of Subject :-

Signature of Investigator :-

Date :-

STUDY RECORDING FORMS

Subject Name..... Study Number

EDINBURGH VEIN STUDY

HEIGHT, WEIGHT & VENEPUNCTURE RECORDING FORM

Date of Examination -- / -- / --

Time of Examination -- . -- am / pm

HEIGHT (without shoes) . cm

WEIGHT (without shoes) . kg

VENEPUNCTURE

- | | NO | YES | D.K |
|--|----------------------|----------------------|----------------------|
| 1. Has the subject ever had Hepatitis or jaundice? | <input type="text"/> | <input type="text"/> | <input type="text"/> |
| If yes, has the subject ever had Hepatitis B? | <input type="text"/> | <input type="text"/> | <input type="text"/> |
| 2. Has the subject ever been told that they are positive for HIV or AIDS or think that they need an AIDS test? | <input type="text"/> | <input type="text"/> | <input type="text"/> |

Comments.....

(TELL THE SUBJECT THAT THE TEST WHICH THEY HAVE TODAY IS NOT AN AIDS TEST.)

IF YES TO EITHER OF THE ABOVE, NO BLOOD IS TO BE TAKEN.

If there is doubt as to the type of Hepatitis and it is more likely to be Hepatitis A, blood can be taken but should be labelled as HIGH RISK.

- | | TRUE | FALSE |
|------------------------------------|----------------------|----------------------|
| Venepuncture was normal | <input type="text"/> | <input type="text"/> |
| Venepuncture was difficult or slow | <input type="text"/> | <input type="text"/> |
| Venepuncture was not possible | <input type="text"/> | <input type="text"/> |

COMMENTS :-.....

Recorded by:- M.C E.K C.E

M.C = Maggie Carson E.K = Eileen Kerracher C.E = Christine Evans

STUDY RECORDING FORMS

Subject Name..... Study Number.....

EDINBURGH VEIN STUDY

LEG EXAMINATION FORM

	RIGHT		LEFT	
	FRONT	BACK	FRONT	BACK
TRUNK / BRANCH				
long saphenous (✓)				
short saphenous (✓)				
uncertain origin (✓)				
RETICULARS				
HYPHENWEB				
C.V.I.				
PITTING OEDEMA	ABSENT / PRESENT		ABSENT / PRESENT	
PERFORATORS				
SCARS (✓)	none		none	
	groin		groin	
	popliteal		popliteal	
	malleolar		malleolar	
	other.....		other.....	
OTHER NOTABLE FINDINGS				

Comments:-

QUESTION : Do you currently suffer from swollen ankles? YES / NO RIGHT / LEFT / BOTH

SUBJECT'S ETHNIC ORIGIN : White Caucasian / African / Indian / Chinese / other

Number of standard photographs taken 3 / 6 /

Specify any problems with the photography.....

Examined by:- M.C E.K C.E
M.C = Maggie Carson E.K = Eileen Kerracher C.E = Christine Evans

STUDY RECORDING FORMS

Subject Name Study Number

EDINBURGH VEIN STUDY

DUPLEX SCANNING RECORDING FORM

Have you ever been investigated for recurrent blackouts or fainting? YES / NO

Are you currently taking any medication for high blood pressure? YES / NO

Procedures	RIGHT		LEFT	
	Operations	Injections	Operations	Injections
Long saphenous	YES / NO	YES / NO	YES / NO	YES / NO
Short saphenous	YES / NO	YES / NO	YES / NO	YES / NO

	1 (secs)	2 (secs)	T (✓)	1 (secs)	2 (secs)	T (✓)
CFV						
SFV origin						
SFV lower 1/2						
Dual SFV						
LSV origin						
LSV lower 1/2						
Pop. upper						
Pop. lower						
SSV						

N.S = vein not seen 0 = no reflux No flow = no flow on augmentation

COMMENTS:-.....

Examined by : M.C E.K C.E P.A

M.C = Maggie Carson E.K = Eileen Kerracher C.E = Christine Evans P.A = Paul Allan

LEG EXAMINATION PROTOCOL

EDINBURGH VEIN STUDY

**PROTOCOL FOR STANDARD PHOTOS AND EXAMINATION
OF LEGS**

EXAMINATION OF THE LEGS

1. The legs will be examined prior to the photography for the presence of varicose veins.
2. The subject will have been standing upright for a minimum of 5 minutes prior to having the legs examined.
3. The subject will stand on the purpose built stand for the examination.
4. The legs will be examined from the back and the front for the presence of the following:-

Trunk veins	grades I-III originating from long saphenous vein, short saphenous vein or origin uncertain
Reticular veins	grades I-III
Hyphenweb veins	grades I-III
Chronic venous insufficiency	grades I-III
Oedema	absent / mild / severe
Scars	groin / popliteal / malleolar / other
Other notable findings	

Where indicated, the above will be classified as grades I-III according to the Basle Study classification (see attached form)

The findings will be documented separately for the front and the back of the legs.

5. The subjects will be asked if they currently suffer from swollen ankles.
6. The subject's ethnic origin will be documented.

LEG EXAMINATION PROTOCOL**PHOTOGRAPHS OF THE LEGS**

1. Following the examination of the legs for the presence of varicose veins, The subject will then have colour photographic slides taken in three standard positions indicated by foot outlines on the surface of the platform:-

1. Facing the camera with the feet out to the side and heels together
2. Back to the camera with the feet out to the side and heels together
3. Back to the camera with the toes pointing straight forward

2. The camera will be positioned to include the area from groin to foot in the photographs ie. at a distance of around 1-1.5 metres.

The aperture will be set at f11-16 or f11 depending on the distance and the colouring of the legs.

The film to be used will be Kodak Ectachrome 200 slide film.

The camera to be used will be a Nikon FM2.

3. Each subject will have their study number placed vertically beside them for identification.

4. The subject will have been standing upright for a minimum of 5 minutes prior to the taking of the photographs.

5. If the subject has had previous surgery for varicose veins, after the initial three standard photographs the sites of the scars will be circled with a water soluble felt pen and three further photographs in the same positions will be taken. If the subject has a scar in the groin, an arrow pointing to the groin will be used to indicate this.

6. The surface of the stand will be covered with clear plastic and will be cleaned following the use by each subject.

7. The number of standard photographs taken for each subject will be documented.

PHOTOGRAPHIC SLIDE EVALUATION FORM

Subject Name..... Study Number.....

EDINBURGH VEIN STUDY
 SLIDE ANALYSIS RECORDING FORM
 FINAL CONSENSUS

	RIGHT		LEFT	
	FRONT	BACK	FRONT	BACK
TRUNK / BRANCH				
long saphenous (✓)				
short saphenous (✓)				
uncertain origin (✓)				
RETICULARS				
HYPHENWEB				
C.V.I				
PERFORATORS				

DUPLEX SCANNING PROTOCOL

EDINBURGH VEIN STUDY

DUPLEX SCANNING PROTOCOL

OBJECTIVE to identify points and patterns of venous incompetence in the deep and superficial veins of the legs

METHODS

Position

- patient lies at an angle of 45 degrees on a tilting couch.

- prior to the examination, each subject is asked:-

- whether they have been investigated or ever suffered from recurrent faints or blackouts

- if they are on any tablets for high blood pressure

If "malignant vasovagal syndrome" has been diagnosed or is a possibility, there is a danger that standing for a prolonged time a tilt may lower the subjects blood pressure, so extreme caution must be observed. If there is any doubt, abandon the examination.

If the subject is on hypotensive drugs, they may not be sufficiently able to compensate for any lowering in blood pressure due to the tilt of the table, and must be told to warn the examiner as soon as they start to feel faint or dizzy.

- If any subject feels faint, dizzy, sick or starts yawning repeatedly while standing on the couch, ask them to COUGH HARD, lower the couch immediately so that the subject is lying flat, offer them a glass of water and do not resume the examination until they feel perfectly all right again.

- to help the examiner, the subject will be asked if they have had previous operations or injections on their veins.

Points to be studied

1. Common femoral vein - above sapheno-femoral junction
2. Superficial femoral vein origin at approx. 2 cm distal to junction with profunda femoris vein
3. Superficial femoral vein - lower third thigh as far down as is reasonable
4. Long saphenous vein - origin
5. Long saphenous vein - lower third thigh as far down as is reasonable
6. Upper popliteal vein - over femoral condyles (above knee crease)
7. Lower popliteal vein - over tibial plateau (below knee crease)
8. Short saphenous vein - origin

DUPLEX SCANNING PROTOCOL

Cuff position	- cuff around calf for all measurements at all vein segments in the first instance. If there is difficulty in obtaining augmentation in the proximal segments (usually the origin of the long saphenous vein) then the procedure should be repeated using the thigh cuff.
Cuff inflation	- to obtain forward flow of blood with a minimal doppler shift of 0.5Hz in the common femoral vein
Duration of inflation	- short inflation as in validation study to mimic hand squeeze - position preset on PGR dial
Duration between inflations	- 5 seconds minimum
Measurement of reflux	<p>- by duration of reflux in seconds. If the reflux goes off the screen the scan speed is reduced to 8 seconds per screen and the reflux elicited again. If the duration of reflux is greater than 8 seconds, then it is documented as ">8".</p> <p>Negatives will be documented as follows :- No reflux = "0". No flow in the vein on augmentation = "No flow". Vein is not seen on the scan = "N.S"</p> <p>If the reflux seen is ambiguous eg. the reflux spectrum is simultaneous with the forward flow spectrum for some or the time, then the duration of reflux suspected is measured as usual for the two measurements and that segment is marked with a "T" for turbulence.</p>
No. of measurements	- mean of two measurements at each of the above points
Further scanning	- anyone we suspect having a deep venous thrombosis (ie. absent or diminished flow in the deep veins or a non-compressible vein) should be asked to come back to be scanned by Dr. P. Allan (either on a Thursday morning or to one of his ultrasound lists). Inability to detect flow in the superficial veins does not carry the same significance and does not require a return visit for a repeat scan.

FOLLOW-UP LETTER TO NON-RESPONDERS



EDINBURGH VEIN STUDY

Wolfson Unit for the Prevention of
Peripheral Vascular Diseases
The University of Edinburgh
Teviot Place
Edinburgh EH8 9AG
Fax 0131 650 6904
Telephone 0131 650 4555

Ref. No. 9~

December 23, 1996

1 ~ 3 ~ 2 ~

4 ~

5 ~

6 ~

Dear 1 ~ 2 ~,

EDINBURGH VEIN STUDY

Sometime during the past two years you received an invitation to take part in the Edinburgh Vein Study. I understand that you decided not to do so.

The study is the first of its kind in the UK and will provide important information about the cause of varicose veins. However, to complete the study we need to know if those who took part were similar to those who did not and for this we **need your help**.

I would therefore be most grateful if you would **fill in the short form enclosed**. Please fill in the form **even if you don't have any problems with your legs** and return it in the prepaid envelope. It should take only a couple of minutes to complete and will help us considerably.

Once we've received your form we will not contact you again.

With many thanks in anticipation.

Yours sincerely,

Dr. Christine J Evans
Clinical Research Fellow

MEDICAL INVESTIGATORS

F G R Fowkes C J Evans P L Allan J M Connor G D O Lowe C V Ruckley

FOLLOW-UP LETTER TO NON-RESPONDERS

Ref No: 9~

EDINBURGH VEIN STUDY

Any information you give in this form is **strictly confidential**. The results of the research will appear only as general statistics from which it will be impossible to identify you as an individual.

Name: 3~ 2~

Please fill in this form by ticking the appropriate boxes.

1. Have you ever been **told by a doctor** that you have or have had any of the following?

	Yes	No
Varicose veins	<input type="checkbox"/>	<input type="checkbox"/>
Leg ulcer	<input type="checkbox"/>	<input type="checkbox"/>
Vein inflammation / phlebitis	<input type="checkbox"/>	<input type="checkbox"/>

2. Do **you** think you have varicose veins?

Yes	No
<input type="checkbox"/>	<input type="checkbox"/>

3. Have you ever had any of the following treatment for varicose veins?

	Yes	No
Operation	<input type="checkbox"/>	<input type="checkbox"/>
Injection of veins	<input type="checkbox"/>	<input type="checkbox"/>
Stockings / bandages	<input type="checkbox"/>	<input type="checkbox"/>

4. Please say why you were unable to take part in the study.
(please tick all the reasons which apply)

Not interested in study	<input type="checkbox"/>
Study a waste of time	<input type="checkbox"/>
Too busy	<input type="checkbox"/>
Clinic times inconvenient	<input type="checkbox"/>
Worried about examination or results	<input type="checkbox"/>
Housebound	<input type="checkbox"/>
Feel healthy so don't need to take part	<input type="checkbox"/>
Already seeing doctor about veins	<input type="checkbox"/>
Forgot about invitation/appointment	<input type="checkbox"/>
Object to invasion of privacy	<input type="checkbox"/>
Other (please give details.....)	

Thank you very much for filling in this form.

PUBLICATIONS

Evans CJ, Fowkes FGR, Hajivassiliou CA, Harper DR, Ruckley CV (1994). Epidemiology of varicose veins – a review. *Int Angiol* 13:263-70. Offprint attached

Evans CJ, Fowkes FGR, Ruckley CV, Allan PL, Lee AJ (1997). Edinburgh Vein Study: Methods and response in a survey of venous disease in the general population. *Phlebology* 12:127-135. Offprint attached

Evans CJ, Allan PL, Lee AJ, Ruckley CV, Fowkes FGR (1998). Prevalence of venous incompetence in the general population on duplex scanning: The Edinburgh Vein Study. *J Vasc Surg* 28:767-76.

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Evans CJ, Fowkes FGR, Ruckley CV, Lee AJ (1999). Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. *J Epidemiol Community Health* 53:149-153.

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Evans CJ, Lee AJ, Ruckley CV, Fowkes FGR (1999). How common is venous disease in the population? In: Fowkes FGR, Ruckley CV, Bradbury AW, editors. *Venous Disease - Epidemiology, Management and Delivery of Care*. Springer Verlag, Cambridge University Press:3-14. Book chapter (not attached)

Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study

C J Evans, F G R Fowkes, C V Ruckley, A J Lee

Abstract

Study objective—To determine the prevalence of varicose veins and chronic venous insufficiency (CVI) in the general population.

Design—Cross sectional survey.

Setting—City of Edinburgh.

Participants—Men and women aged 18–64 years selected randomly from age-sex registers of 12 general practices.

Main results—In 1566 subjects examined, the age adjusted prevalence of trunk varices was 40% in men and 32% in women ($p \leq 0.01$). This sex difference was mostly a result of higher prevalence of mild trunk varices in men. More than 80% of all subjects had mild hyphenweb and reticular varices. The age adjusted prevalence of CVI was 9% in men and 7% in women ($p \leq 0.05$). The prevalence of all categories of varices and of CVI increased with age ($p \leq 0.001$). No relation was found with social class.

Conclusions—Approximately one third of men and women aged 18–64 years had trunk varices. In contrast with the findings in most previous studies, mainly conducted in the 1960s and 1970s, chronic venous insufficiency and mild varicose veins were more common in men than women. No evidence of bias in the study was found to account for this sex difference. Changes in lifestyle or other factors might be contributing to an alteration in the epidemiology of venous disease.

(J Epidemiol Community Health 1999;53:149–153)

difficult to determine, because relatively few population-based epidemiological studies have been carried out. Many previous studies have investigated samples of clinic patients or specific occupational groups, and comparison of results is further hampered by a lack of uniform definitions and methods of measurement.² Many of the studies were conducted over 20 years ago and the reported prevalence of varicose veins ranges widely from 0.1% in women living in rural New Guinea³ to 68% in female chemical workers in Basle, Switzerland.⁴ It is estimated that chronic leg ulceration affects 1% of the population at some point in their lives⁵ and surveys have shown that 57–80% of leg ulcer patients have demonstrable venous disease.⁶

The Edinburgh Vein Study is the first large scale study of its kind in the United Kingdom to investigate venous disease in the general population. The aims of the study were to determine the prevalence of venous disease of the legs in a randomly selected population sample, and to investigate associations with certain genetic and lifestyle factors. Lifestyles of men and women have changed greatly in the UK since the 1960s and 1970s when many of the previous epidemiological studies were conducted, and such changes might have affected the occurrence of disease. Given recent concerns about the priority accorded to the treatment of varicose veins in the NHS, the purpose of this paper is to provide up to date information on the prevalence of varicose veins and chronic venous insufficiency in the general population.

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Venous disorders of the legs occur frequently, and range in severity from minor asymptomatic incompetence of venous valves to chronic leg ulceration. Varicose veins are a common manifestation of venous incompetence in the lower limb, and appear as dilated, elongated or tortuous superficial veins. Incompetence of the deep, superficial and/or perforating veins leads to raised venous pressure in the lower leg, which can result in skin changes such as hyperpigmentation and induration with eventual ulceration. These changes in the skin and subcutaneous tissues of the lower leg are often referred to clinically as chronic venous insufficiency (CVI).

Venous disease of the legs causes considerable morbidity and is also costly, with approximately 2% of national healthcare resources being spent on treatment.¹ Exactly how common varicose veins are in the community is dif-

Methods

The Edinburgh Vein Study is a cross sectional survey, with a target population comprising men and women aged 18 to 64 years, resident in Edinburgh. An age stratified random sample was selected from the computerised age-sex registers of 12 general practices, whose catchment areas were geographically and socioeconomically distributed throughout the city. A total sample size of 1500 participants was estimated, based on the number required to give an adequate precision for prevalence, to detect a significant difference in prevalence between groups and to enable a subsequent follow up study to be conducted. Details of the methods and response in the Edinburgh Vein Study have been reported.⁷

Subjects attended a clinic in the University of Edinburgh and were examined by one or more members of a research team, comprising

a nurse, technician, and clinical research fellow. A self administered questionnaire was completed that included personal and occupational details, relevant medical and family history and possible risk factors for venous disease. The method of examination and classification of venous disease used in the Edinburgh Vein Study was adapted from the method used in the Basle Study,⁸ as this was considered to be the best available⁹ and to provide the most detailed classification for the different degrees of varicose veins. During inspection of the legs, subjects stood on a raised platform with their feet in three standard positions: facing towards the examiner with heels together and forefeet spread wide apart, facing away from the examiner in a similar position, and facing away from the examiner with feet parallel. They were asked to remain in a standing position for a minimum of two minutes before examination of their veins, to allow the blood to pool in the legs. Any scars and notable findings on the legs were recorded.

Varices were divided into three types; trunk varices, reticular varices and hyphenweb varices. Trunks were defined as "dilated, tortuous trunks of the saphena magna or parva vein and their branches of the first or second order", reticulars as "dilated, tortuous subcutaneous veins not belonging to the main trunk or its major branches", and hyphenwebs as "intra-dermal varices". Each of the three groups was sub-divided into grades of severity 1-3, determined according to the "degree and extent of tortuosity and prominence of the veins".⁸ These grades were determined with reference to photographs from the Basle study. In practice, grade 1 trunks ranged from a small discrete visible or palpable length of dilated trunk vein to more obvious but not grossly dilated varicose veins; grade 2 trunks were more extensive and/or more grossly dilated trunk varices and grade 3 trunks were varices at the most severe end of the spectrum. Each subject was also examined for presence of any pitting ankle oedema, and assessed for CVI as defined in the Basle Study.⁸ Grade 1 CVI was defined as "dilated subcutaneous veins/corona phlebectatica", grade 2 CVI as "hyper- or depigmented areas, with or without corona phlebectatica", and grade 3 CVI as "open or healed ulcer cruris". The recently developed CEAP classification for chronic venous disease¹⁰ was not available when the Edinburgh Vein Study began. However, the above grades of CVI correspond to the CEAP clinical classification as follows: grade 1 CVI corresponds to Class 1 (malleolar flare), grade 2 CVI corresponds to Class 4 (skin changes), and grade 3 CVI corresponds to Classes 5 and 6 (healed or active ulceration).

As in the Basle Study,⁸ photographs of the legs were taken. The photographic slides were subsequently independently analysed according to the classification system described above, by the two study team members who had not seen the patient in the clinic. Discrepancies of two or more grades between the two observers were resolved by discussion with an experienced clinician (CVR). This process

resulted in two independent classifications of the venous status of each subject:- one based on examination in the clinic, and the other on analysis of the photographic slides. The results in this paper are based on the examination findings. In addition, a comparison of the two methods of classification is reported. Quality control measures for this classification procedure included weekly analysis and discussion of the photographic slides, periodic review of reference photographs as a reminder of the original standard and, periodically throughout the study, independent examination of the same volunteers by all three team members to allow identification and discussion of discrepancies.

After each subject's appointment, a report of the clinical findings was sent to their general practitioner. Those subjects wishing more information on varicose veins were offered an advice leaflet¹¹ and referred back to their general practitioner. Nineteen subjects had a "home visit" appointment because of their inability to attend the university clinic for medical or social reasons. Local ethics committee approval was given for the study and informed consent was obtained from each study participant.

A survey was carried out of the "non-responders" (that is, those subjects who initially agreed to participate in the study and subsequently withdrew or failed to attend their appointment, and those subjects who declined to participate in the study from the beginning) from 4 of the 12 practices. This survey took the form of a one page questionnaire, inquiring about past history of venous disease and treatment for varicose veins. For each non-responder, demographic data were available and a Carstairs deprivation score was derived from the individual's postcode.^{12,13}

Information from the recording forms and questionnaires were entered onto a DBASE IV database. The data files were transferred to the Edinburgh University Mainframe computer for analysis using the SPSS-X and SAS statistical packages. The following statistical tests were used:- χ^2 test and Mantel-Haenszel test for linear association for categorical data, the Mann-Whitney test for continuous non-parametric data and the κ statistic as a measure of agreement between categorical variables.¹⁴ The age adjusted prevalence rates were calculated using GLIMMIX (a SAS macro), which fits generalised linear mixed models.

Results

A total of 1566 subjects attended for examination, 867 women and 699 men, resulting in a response rate of 53.8% for those contacted and still living in the area.⁷ The age adjusted prevalence of trunk varices (grades 1-3) was 39.7% in men and 32.2% in women ($p \leq 0.01$). Table 1 shows that the majority of affected subjects had mild (grade 1) trunks and the difference between the sexes reached statistical significance for grade 1 only ($p \leq 0.01$). Hyphenweb and reticular varices were very common, each affecting over 80% of subjects, although the majority had these varices only to a mild degree (grade 1). Among the smaller numbers affected

Table 1 Age adjusted prevalences of grades of varices and chronic venous insufficiency (CVI) by sex

	Grade	Men (n=699)		Women (n=867)		p value
		%	(n)	%	(n)	
Trunk varices	1	33.3	(238)	26.2	(223)	0.009
	2	5.4	(39)	5.6	(47)	0.888
	3	1.0	(7)	0.5	(4)	0.241
Hyphenweb varices	1	79.2	(554)	84.4	(732)	0.260
	2	5.9	(44)	9.2	(76)	0.030
	3	0	(0)	0.6	(5)	—
Reticular varices	1	81.6	(571)	85.3	(739)	0.422
	2	4.0	(29)	6.4	(54)	0.042
	3	0	(0)	0	(0)	—
CVI	1	6.9	(51)	5.3	(44)	0.157
	2	1.3	(10)	1.1	(9)	0.607
	3	1.0	(8)	0.2	(2)	0.058

(n) = number in each group with varices/CVI.

by grade 2 hyphenweb and reticular varices, women had significantly higher prevalences than men (both $p \leq 0.05$). The age adjusted prevalence of chronic venous insufficiency (grades 1–3) was 9.4% in men and 6.6% in women ($p \leq 0.05$). However, sex differences were not statistically significant when the grades of severity were analysed individually ($p > 0.05$). A total of 10 subjects (8 men and 2 women) had current or previous venous ulceration (grade 3 CVI).

Table 2 shows the prevalence of trunk varices by age group. The prevalence increased linearly with age in both sexes, and ranged from 11.5% in the 18–24 year olds to 55.7% in the 55–64 year olds when both sexes were combined ($p \leq 0.001$). Likewise, the prevalence of both reticular and hyphenweb varices increased linearly with age in both sexes ($p \leq 0.001$). Table 3 shows that, under the age of 35 years, CVI was extremely rare in women and did not occur at all in men. Overall, the prevalence of CVI increased markedly with age ($p \leq 0.001$). In the oldest age group of 55–64 years, the prevalence of CVI was much higher in men (25.2%) than women (12.3%) ($p \leq 0.001$). However, even in this age group, most of those affected had only mild (grade 1) CVI (18.3% of men and 8.6% of women). The age adjusted prevalence of pitting ankle oedema was 7.4% in men and 16.0% in women ($p \leq 0.001$) and increased linearly with age ($p \leq 0.001$).

There was no obvious relation between social class (classified by occupation) and the age and sex adjusted prevalences of either trunk varices or CVI (table 4). The age and sex adjusted prevalence of both conditions was higher in manual workers (social classes IIIIM–V) than non-manual workers (social classes I–IIIN) but these differences were not statistically significant (both $p > 0.05$).

A slide classification of venous status based on analysis of photographic slides was available

for 1555 of the 1566 subjects in the study. The classifications of venous status based on (a) examination in the clinic and (b) analysis of the slides were compared, in each case taking the leg with the higher grade as the patient's score. There was "fair to good agreement"¹⁴ for trunk varices ($\kappa = 0.60$) and CVI ($\kappa = 0.64$) between the two classification methods.

The age adjusted prevalences of trunk varices and CVI reported by the two principal observers were compared. Observer 1 classified 35.9% of subjects as having trunk varices and 8.2% as having CVI, compared with 36.7% and 8.0% respectively for observer 2 (both $p > 0.05$). When further analysed by sex, the age adjusted prevalences of trunks and CVI, as classified by observers 1 and 2 respectively, were as follows; trunks: men 43.2% v 42.2% ($p > 0.05$), women 31.2% v 33.1% ($p > 0.05$); CVI: men 11.5% v 10.1% ($p > 0.05$), women 6.0% v 6.8% ($p > 0.05$).

There was a total of 1346 "non-responders"—that is, 998 who refused to participate and 348 who agreed take part in the study but subsequently withdrew. The non-responders were generally younger, lived in relatively less affluent postcode sectors^{12,13} and contained a higher proportion of men than the study attenders (all $p \leq 0.001$).⁷ A one page questionnaire inquiring about venous disease was sent to 378 non-responders from 4 of the 12 participating general practices and 194 (51.3%) of these questionnaires were returned. There were no significant differences between those who returned and did not return their questionnaires with regard to sex and age band (both $p > 0.05$), but the non-responders who returned their questionnaires lived in relatively more affluent postcode sectors than those who did not return them ($p \leq 0.05$). The non-responders' questionnaire results were compared with the results of study attenders from the same four practices who answered the same

Table 2 Prevalence of trunk varices by age and sex

	Age (y)										
	18–24		25–34		35–44		45–54		55–64		p value
	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	
Men	20.0	(11)	15.5	(16)	36.1	(57)	42.0	(76)	61.4	(124)	0.000
Women	5.3	(4)	13.9	(22)	22.6	(42)	41.9	(95)	50.5	(111)	0.000
Total	11.5	(15)	14.6	(38)	28.8	(99)	41.9	(171)	55.7	(235)	0.000

(n) = number in each group with varices. Trunk varices include grades 1–3. p values based on Mantel-Haenszel test for linear association.

Table 3 Prevalence of chronic venous insufficiency (grades 1-3) by age and sex

Age (y)	Men			Women		
	(n)	%	95% CI	(n)	%	95% CI
18-24	(0)	—	—	(1)	1.32	0.03, 7.11
25-34	(0)	—	—	(2)	1.25	0.15, 4.44
35-44	(4)	2.53	0.69, 6.28	(7)	3.76	1.48, 7.48
45-54	(14)	7.73	4.31, 12.74	(18)	7.93	4.87, 12.52
55-64	(51)	25.25	19.25, 31.62	(27)	12.27	8.17, 17.20

(n) = number in each group with CVI.

Table 4 Age and sex adjusted prevalence of trunk varices and chronic venous insufficiency (CVI) by social class

Social class	Trunk varices		CVI	
	%	(n)	%	(n)
I	35.0	(43)	5.6	(6)
II	35.8	(185)	7.5	(39)
IIIN	32.2	(113)	7.0	(24)
IIIM	43.4	(91)	13.3	(29)
IV	33.4	(33)	10.1	(9)
V	40.0	(32)	8.1	(8)

Both trunk varices and CVI include all grades (1-3). (n) = number in each group with varices/CVI. Social class based on occupation. Based on a total = 1376. Excluded are housewives (123), students (56), armed forces (6), unemployed with no previous job (2), and missing data (3).

questions in the main study questionnaire. After adjusting for age and sex, 6.5% of the 194 non-responders who returned their questionnaire reported a doctor's diagnosis of varicose veins compared with 13.3% of the attenders ($p \leq 0.05$). Of the men, 6.7% of non-responders and 9.1% of attenders reported a doctor's diagnosis of varicose veins ($p > 0.05$) compared with 6.5% of non-responders and 16.7% of attenders among the women ($p \leq 0.05$). Extrapolation of this information to all the non-responders in practices 1-4 suggests that a higher proportion of women than men with a doctor's diagnosis of varices attended, while a similar proportion of men and women without a doctor's diagnosis attended (data not shown).

Discussion

Results from the Edinburgh Vein Study confirm that venous disease is common in the general population, with approximately one third of the study population showing some degree of trunk varicose veins. In addition, the vast majority of subjects had a mild degree of hyphenweb and reticular varices, suggesting that these minor stigmata are "the norm". An increase in varices with age was demonstrated, in common with findings from many other studies.²⁻⁹

The major unexpected finding from this study was the significantly higher prevalence of trunk varicose veins in men compared with women. This significant difference was largely because of a higher prevalence of mild (grade 1) varices in men. Men also had a higher prevalence of chronic venous insufficiency (grades 1-3) than women, although the sex differences were not significant when grades of CVI were analysed individually. Conversely, women had a higher prevalence of moderate (grade 2) hyphenweb and reticular varices, and of pitting ankle oedema, than men.

KEY POINTS

- Trunk varicose veins are common, occurring in approximately one third of the adult population.
- Hyphenweb and reticular varices are "the norm" occurring in over 80% of the population.
- Mild trunk varices are more common in men than women in this study population (33.3% versus 26.2%) in contrast with findings from many previous studies.
- Prevalence of venous disease is not significantly related to social class.
- Changes in lifestyle may be affecting the epidemiology of venous disease.

Most of the evidence from previous studies indicates a higher prevalence of varicose veins in women. It has been suggested that variation in the sex ratio between different studies may be partly because of differences in the age of the populations studied and the methods of measurement used.⁹ However, many of the results on overall prevalence from previous studies were not adjusted for age, and this factor may have obscured any true sex differences. Also, studies that relied on self assessment of varicose veins or reporting of a previous diagnosis by a physician, may have been prone to bias, because women may have been more likely to report varices or to consult their doctor for this condition than men. This hypothesis is supported by the Edinburgh Vein Study finding that only 10% of men reported a previous doctor's diagnosis of varicose veins in their questionnaire compared with 17% of women. Men were subsequently found to have a significantly higher prevalence of trunk varices than women on examination.

The Basle Study (the origin of the method of classification used for the Edinburgh Vein Study) found a similar prevalence of all varices in men and women, but the sample contained relatively few women.⁸ The small number of published studies that have examined population samples have all found a higher prevalence of varices in women than men.¹⁵⁻¹⁷ Abramson *et al* surveyed residents of a Jewish neighbourhood of Western Jerusalem and found that the age standardised prevalence for varicose veins (excluding venectasias) was 29.5% in women and 10.4% in men.¹⁵ In the Tecumseh Community Health Study, a longitudinal study of a total USA community, the overall prevalence of "any varicose veins" was 25.9% in women and 12.9% in men, and although these figures were not age standardised, the prevalence of varices was higher in each age group in women.¹⁶ Leipnitz *et al* examined a sample of 2821 subjects aged 45-65 years, randomly selected from the greater Aachen district and found the prevalence of varicose veins to be 29.0% in women and 14.5% in men.¹⁷ However, in a recent study in South Wales in which 600 randomly selected men and women over the age of 60 years were examined, sex was not a significant risk factor for varicose veins (I Harvey, personal communication). In another

recent study in Bochum, Germany, children were examined on three occasions during their school education. By the age of 18–20 years, men had a higher prevalence of trunk varices, tributary varices, and incompetent perforators than women, while women had a higher prevalence of reticular varices and telangiectasias (hyphenwebs).¹⁸ Although no tests of significance were reported on these results, the sex differences followed a similar pattern to that seen in the Edinburgh Vein Study.

In the Edinburgh Vein Study, the question that arises therefore is whether the prevalence of varicose veins in men was really higher than in women, or whether this result was caused by bias. Differential measurement error was unlikely because the method used to identify venous disease was based on a standardised classification,⁸ and showed "fair to good" agreement with a second objective classification based on colour photographs.¹⁴ Furthermore, the two principal observers classified almost identical proportions of men and women as having trunk varices and CVI. Also, in another paper, we have reported that venous incompetence measured by duplex scanning was significantly more common in the deep veins in men than in women.¹⁹ Alternatively, the results may have been biased if men with varices were more likely to attend than women with varices. However, comparison of the prevalence of doctor's diagnosis of varices in the male and female non-responders and attenders suggests that this was unlikely.

If the prevalence of varicose veins was truly higher in men than women in this population, it may be that changes in lifestyle, working practices or the environment have led to a change in the difference in prevalence between the sexes. The evidence to support any association between varices and many lifestyle factors such as prolonged standing, tight undergarments, toilet posture, chair sitting, and dietary fibre intake is lacking.⁹ However, the available evidence suggests that the prevalence of varicose veins increases with increasing numbers of pregnancies.⁹ Perhaps the general tendency for women to have fewer children later in life has resulted in a lower prevalence of varices in this relatively young group of women. Detailed analysis of the association between lifestyle factors such as pregnancy, hormone use, and dietary fibre intake and the presence of varicose veins and CVI in the Edinburgh Vein Study population will be examined in future papers.

In conclusion, venous disease is a common condition in the young and middle aged. This study suggests that mild varicose veins are more common in men, but there are insuffi-

cient data at present to comment on the sex differences in severe venous disease. We have identified no evidence to suggest that the higher prevalence in men is the result of bias in the study, although such bias cannot be ruled out in studies such as this. Follow up of this cohort will provide information on the natural history and development of venous disease in both sexes, and the resulting implications for patients and the provision of healthcare.

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Epidemiology of varicose veins

A review

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Disease of the venous system is a major problem affecting western societies, resulting in considerable morbidity in the population and cost to the health service. In many countries "varicose veins are probably the commonest disorder presenting to general surgeons"¹ and an average of 30% of district nursing time is estimated to be spent caring for patients with venous ulcers.² For the patient with varicose veins or leg ulceration, there is often persistent discomfort and disability extending over long periods of time. Despite this, little epidemiological research has been carried out on venous disease, perhaps partly because of society's perception that venous disease is not a major problem and it is not normally a cause death. More recently however, efforts have been made to conduct structured epidemiological studies to identify risk factors and to clarify the geographical variations suggested in the past by anecdotal evidence. This article reviews recent epidemiological studies, discusses the prevalence of varicose veins and presents evidence for and against the differing theories of causation. [Int Angiol 1994; 13:263-70].

Key words: Varicose veins - Epidemiology.

Methodological problems

In comparing the results of epidemiological studies, several methodological issues have to be considered.

Definitions

Firstly, there is no accepted standard definition of varicose veins. Several investigators have

used the definition described by Arnoldi³ "...any dilated, elongated, or tortuous veins, irrespective of size".⁴⁻⁹ Mekky *et al.*¹⁰ used the definition of Dodd & Cockett, "...A varicose vein is one which has permanently lost its valvular efficiency. ...As a result of continuous dilation under pressure in the course of time a varicose vein becomes elongated, tortuous, pouched and thickened."¹¹ An important variation in definitions was the specific inclusion^{6 12-14} or omission^{7 10 15 16} of intradermal (hyphenweb) veins and small subcutaneous (reticular) veins (Table I). This difference makes direct comparison of these two groups of studies difficult.

Methods of measurement

Methods of measurement differed among the studies. Nearly every study included a history and examination, and in some, the history was standardised using questionnaires.^{7 8 10 14 17 18} In relation to family studies, Weddell has shown that a history from the proband is an invalid method of determining prevalence in other family members and she demonstrated that examination of relatives yielded vastly different results in comparison with those obtained on questioning.¹⁸

In other studies attempts were made to standardise the conditions under which examinations were performed e.g. resting the subject prior to examination.⁹ Most studies had subjects standing during the examination. Other attempts at standardisation of methods included the submis-

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TABLE I.—Prevalence of varicose veins in males and females from epidemiological surveys in several countries.

Country	Year	Population	Definition used	No.	% female	% male
Brazil ⁷	1986	Health centre patients	Excl. HW & mild retics	1755	50.9	37.9
Cook Is Pukapuka ⁴	1975	Selected population	All varicosities	377	4.0	2.1
Cook is Rarotonga ⁴	1975	Selected population	All varicosities	417	14.9	15.6
Czechoslovakia ¹⁴	1981	Shop employes	All varicosities	696	60.5	—
Denmark ³	1957	Hospital patients	All varicosities	293	48.8	—
Egypt ¹⁰	1969	Cotton mill workers	Excl. hair veins & SW	467	5.8	—
England ¹⁰	1969	Cotton mill workers	Excl. hair veins & SW	504	32.1	—
India (North) ⁸	1972	Railway sweepers	All varicosities	354	—	6.8
India (South) ⁸	1972	Railway sweepers	All varicosities	323	—	25.1
Israel ¹⁵	1981	Population sample	Excl. very small varicosities	4888	29.3	10.4
Japan ⁶	1990	Patients, hospital staff, elderly residents	All varicosities	541	45.0	—
New Guinea ⁹	1975	Villagers	All varicosities	1457	0.1	5.1
N. Zealand (Maori) ⁴	1975	Selected population	All varicosities	721	43.7	33.4
N. Zealand (Euro) ⁴	1975	Selected population	All varicosities	356	37.8	19.6
Sicily ⁴⁴	1988	Villagers	All varicosities	1122	46.2	19.3
Switzerland ¹²	1967	Chemical industry employes	All varicosities	4376	68.0	57.0
Switzerland ²⁰	1973	Chemical industry employes	All varicosities	4529	55.0	56.0
Switzerland ¹³	1973	Shop and factory employes	Excl SW & mild retics	610	29.0	—
Tanzania ⁵³	1977	Outpatients	All varicosities	1000	5.0	6.1
Tokelau Island ⁴	1975	Selected population	All varicosities	786	0.8	2.9
United States ¹⁷	1973	Population sample	All varicosities	6389	25.9	12.9
Wales ¹⁸	1966	Population sample	All varicosities	289	53.1	37.2

Excl. = excluding; HW = hyphenwebs; retics. = reticular veins; SW = spiderwebs.

sion of examiners and interviewers to initial training,⁷ the use of only one observer,^{8, 10} joint classification by two observers,¹⁹ and review of diagnoses by a senior physician prior to final documentation.¹⁷

In a major study conducted in Basle, in addition to physical examination three coloured photographic slides were taken under standardised conditions. These were then analysed by a team of examiners.²⁰ This method was adopted by Hirai *et al.* as an additional measurement in patients diagnosed as having varicose veins on examination.⁶

Stvrtinova *et al.* used continuous wave Doppler measurement for assessing patency and valvular function,¹⁴ and Doppler ultrasound was used to detect presence of presymptomatic venous reflux in schoolchildren in the Bochum study.²¹

Prevalence of varicose veins

Table 1 shows the prevalence of varicose veins observed in studies conducted in different countries. The study populations varied widely and there was no standard definition of varicose veins. Some authors included all sizes of varices

("all varicosities") while others excluded some of the smallest e.g. hyphenwebs or reticular varices ("exclusions"). Given these reservations, the prevalences varied markedly from 0.1% in females living in villages in rural New Guinea,⁹ to 68% in female workers in the chemical industry in Basle, Switzerland.¹²

Age

A common finding in epidemiological studies was that the prevalence of varicose veins increased with age, for example, among English female cotton workers in the 1960's, from 7% in those aged 15-25 years to 45% in those aged 45-55 years (Fig. 1).¹⁰ In the Bochum study, examination of a cohort of schoolchildren aged 10-12 years demonstrated the presence of discrete reticular varices only in 10% of the pupils, but four years later this figure had increased to 30%, and a number of children had developed stem and branch varices.²¹ Childbirth and body weight both appeared to be risk factors for varicose veins in a study of Swiss women but not when the relationships were adjusted for age.¹³ Age must therefore be taken into account when investigating possible risk factors.

Geographical variations

Several authors have produced anecdotal evidence derived from their clinical observations in Third World countries, suggesting that varicose veins are rare in Africa and other developing countries in comparison with the West.²²⁻³⁰ However, this difference was disputed by Rougemont who found the relatively high prevalence of 10.9% in women living in villages in the Republic of Mali.³¹ Rivlin believed that there was an equal prevalence throughout the world but the occurrence of fewer complications in tropical Africa resulted in the condition presenting very rarely.³² This theory was supported by the results of a survey by Daynes and Beighton, who found a prevalence of 7.7% among women in the Transkei, South Africa. Despite this higher than expected prevalence, none of the women complained of any symptoms.³³

Other studies have suggested that race may be important for the development of varicose veins. A survey in Jerusalem showed that immigrant men born in North Africa had a significantly lower age adjusted prevalence rate for varicose veins than immigrants from Europe, America and Israel.¹⁵ Prevalence was shown to vary among women from different parts of Europe;¹³ furthermore Japanese women seemed to have a prevalence between that of Europeans and Africans;⁶ and English women cotton workers had a much higher prevalence than their Egyptian counterparts (Table I).¹⁰

Sex differences

In most epidemiological surveys the prevalence has been found to be higher in females than in males (Table I). In some studies this sex difference appeared greatest in the younger age groups and fell with increasing age.^{4 34} However, in Switzerland¹² and among the Rarotongan Cook Islanders⁴ no sex difference was found. On the other hand, males were found to have a higher prevalence in New Guinea,⁹ Kenya³⁵ and Hong Kong.³⁶ It has been suggested that the prevalence rises first in males in developing countries due to their earlier contact with Western culture. Alternatively the higher prevalence in women in the West has been blamed on their tendency to seek medical help, for cosmetic reasons, earlier than men.³⁷

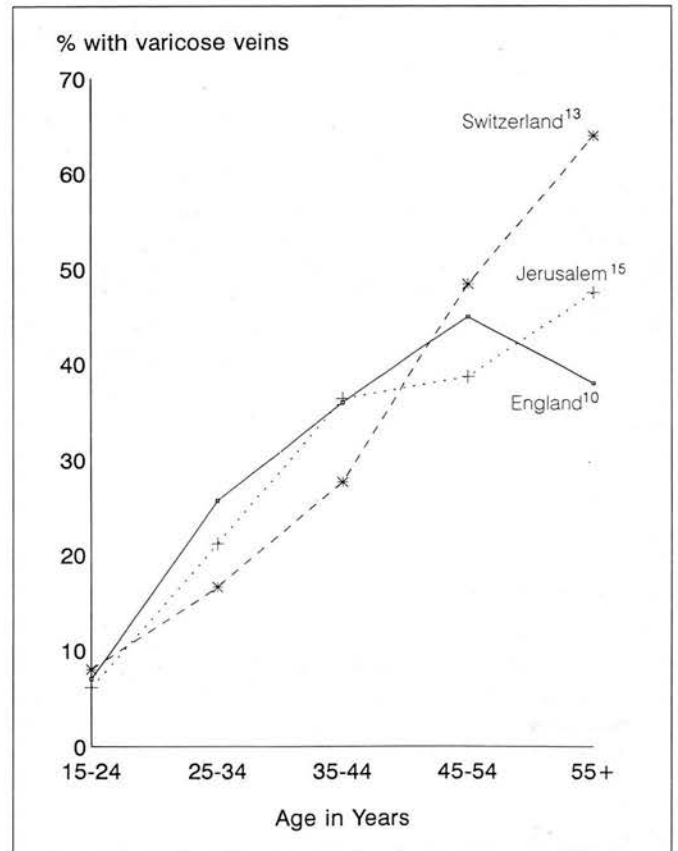


Fig. 1.—Prevalence of varicose veins in women by age in studies from England, Jerusalem and Switzerland. Calculated from: Mekky *et al.*¹⁰ Abramson *et al.*¹⁵ and Guberan *et al.*¹³.

Disorder or disease?

In patients with varicose veins, the distinction between “disorder” and “disease” is necessary in order to obtain a realistic picture of the importance of the condition.³⁸ In the Basle study, the 12% of subjects judged as having varicose “disease” were further subdivided into those with “pathological varicosity” (3%) and those with “relevant varicosity” (9%).³⁹ Both of these groups were shown to have suffered an increased incidence of complications and socio-medical consequences compared with the non-diseased groups.

Thus, when considering the prevalence of varicose veins it is important to note that while a large percentage are of little medical importance, those patients with true varicose disease suffer complications, seek medical treatment and have considerable socio-economic implications.

Aetiology

Inherited or acquired?

The fundamental question with regard to the aetiology of varicose veins is whether the primary defect is inherited and thus inevitable, or acquired and therefore potentially preventable.⁴⁰

Gunderson and Hauge investigated the role of heredity in the aetiology of varicose veins.³⁴ They found that the risk of varicose veins was higher in those with affected relatives and if the relative was a male. Hirai *et al.* also found an increased prevalence in relatives of patients with the condition.⁶ However, both studies relied on the proband's history for the assessment of relatives, and this method has been shown to be highly inaccurate by Weddell.¹⁸ The numbers in her own study were too small to reach any conclusions about the heredity of varicose veins.

Thus the few studies on heredity are inconclusive and the findings do not seem to fit with any single genetic model of inheritance.⁴¹ A study on the cadavers of black Africans showed that they have a higher number of valves than Caucasians when comparing the same section of leg vein.⁴² This suggests that the number of valves is an inherited factor differing between races and may account for the differences in prevalence of varicose veins seen in different parts of the world.

A strong argument against a primary genetic cause of varicose veins however is the case of black Americans. Whereas the prevalence of varicose veins in Africans is generally accepted as being lower than that in Westerners, the prevalence is equal among black and white Americans⁴³ i.e. immigrants from an area of supposedly low prevalence have acquired the high prevalence of their adopted country, suggesting an environmental rather than a hereditary cause. If the greater number of valves in black Africans was responsible for their protection from the development of varices, then the prevalence would not be expected to have increased, despite their change in environment.

Acquired theories of causation

Many environmental factors have been suggested as contributing to the development of var-

icose veins, in support of the theory of acquired causation. The following potential risk factors have been identified:

Parity.—In New Zealand women of European origin, a greater number of pregnancies has been associated with an increasing prevalence of varicose veins, and in Maoris with a greater severity of varicose veins.⁵ Maffei *et al.* also found a positive correlation between prevalence of varicose veins and number of previous pregnancies, independent of age,⁷ while Abramson found this was true only in the 24-35 year age group.¹⁵

Several studies have shown that parous women have a higher prevalence of varicose veins than nulliparous women,^{14 44} but Hirai *et al.* found that this was only significant in younger women.⁶ Guberan *et al.* discovered no correlation between previous pregnancy and prevalence of varicose veins when results in a study of Swiss women were corrected for age.¹³

The widely held belief that pregnancy leads to varicose veins due to the pressure of the pregnant uterus obstructing venous return from the legs, has been refuted, because the majority of varices appear during the first three months of pregnancy when the uterus is not large enough to cause mechanical obstruction.³ Arnoldi suggested that a hormonal factor may be responsible³ while Fanfera *et al.* pointed out that the additional burden of the increased circulating volume of blood in the veins could be a significant factor during pregnancy.⁴⁵

The evidence for a relationship between varicose veins and pregnancy is thus inconsistent and it has been suggested that pregnancy may merely be an exacerbating factor in those already predisposed, rather than a primary cause.⁴⁶

Body mass, weight and height.—Opinions vary on the importance of body mass, weight, and height in the development of varicose veins. Obesity is a commonly quoted factor and was found to be significantly more common in younger men and women with varicose veins in Israel¹⁵ but not in a study of Swiss women, after correction for age.¹³ Height, but not weight or body build, was associated with a significant increase in the prevalence of varicose veins in a retrospective study of English men,⁴⁷ while in

TABLE II.—Comparison between spontaneous clot-lysis and clotting time in sweepers with varicose veins versus those with no varicose veins, from Madras (South India) and Ajmer (North India).

Groups	With varicose veins			Age matched controls with no varicose veins		
	n of men	% showing clot-lysis	Mean clotting time in minutes \pm SE	n of men	% showing clot-lysis	Mean clotting time in minutes \pm SE
Madras (South Indians)	81	3.7	8.66 \pm 0.14	81	37.4	8.40 \pm 0.16
Ajmer (North Indians)	24	25.0	9.0 \pm 0.25	24	83.2	8.77 \pm 0.13

Statistically significant difference in the occurrence of spontaneous clot-lysis between those with varicose veins as compared with healthy controls in both the South and North Indian groups ($p \leq 0.001$) but no differences in the mean clotting time.

Source: Malhotra SL.* Reproduced with permission of the editor, International Journal of Epidemiology.

Maori males all three physical characteristics were associated with varicose veins.⁵

Posture at work.—Prolonged standing has often been blamed for the development of varicose veins.

Standing at work was shown to have a positive association with varicose veins in the study in Israel¹⁵, a finding supported by others.³⁵⁻⁴⁷ However among women in Czechoslovakia, an association with standing was found only for varices of the main trunk veins.¹⁴ In the Framingham Study the two year incidence of varicose veins was higher with the length of time women spent sitting or standing¹⁶ but no significant difference was found relating posture to varicose veins in a study from Brazil.⁷ In a study of railway sweepers in North and South India, both groups were engaged in the same job, and therefore posture at work could not account for the observed difference in prevalence.⁸

Cleave dismissed the theory that man's erect posture is the cause of varicose veins arguing that all the other structures in the body i.e. arms, legs, feet and hands, have adapted and it is therefore inconceivable that the leg veins would not.⁴⁸ Also this theory would not explain the geographical differences which exist. Burkitt and Geelhoed argued that prolonged standing and pregnancy cannot be primary causes because Africans spend more time on their feet and have more pregnancies than those in the West, where the prevalence is higher.³⁷⁻⁴⁹⁻⁵⁰

Tight undergarments.—In the study of cotton workers in England and Egypt in the 1960's the prevalence of varicose veins increased with the tightness and stiffness of the undergarment being worn.¹⁰ Also in Jerusalem habitual corset-

wearing was a positive risk factor,¹⁵ supporting the theory that raised intra-abdominal pressure may be important in the aetiology of varicose veins. However Guberan *et al.* found that correcting for age eliminated the association of corset-wearing with varicose veins in a sample of Swiss women.¹³

Haematological factors.—In the study of Indian railway sweepers, it was found that South Indians, who had an increased prevalence of varicose veins compared with North Indians, had a lower blood clotting time and less spontaneous clot lysis than those in the North.⁸ However when comparing those with varicose veins to normal controls only the lower clot lysis was found to be significantly different (Table II). It was suggested that these differences were diet related, as the South Indians consumed more long-chain fatty acids, said to be associated with enhanced blood coagulation.

Diet and constipation.—Cleave suggested that varicose veins develop as a result of constipation which is predominantly a manifestation of a Western diet. Constipation was found to be a positive risk factor for the development of varicose veins in the Sicilian study⁴⁴ but not in female cotton workers from Egypt and England,¹⁰ nor in the Kenyan study.³⁵

The refined Western diet contains much less fibre than the diet of traditional Africans. This results in larger harder stools which are more difficult to pass, thus leading to regular straining and repeated increases in intra-abdominal pressures.⁴⁹ The greater the "Westernisation" of primitive peoples, the more refined their diet. The prevalence of varicose veins appears to increase in line with "Westernisation" e.g. in the

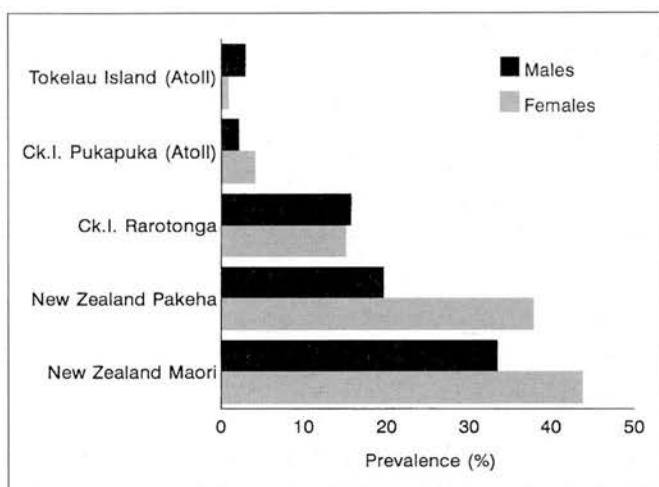


Fig. 2.—Age standardised prevalence rates of varicose veins in males and females in the South Pacific. Source: Adapted from Beaglehole *et al.*⁴ Produced with permission of the author.

Pacific, the prevalence of varicose veins in Atoll dwellers was low in comparison to the Rarotongans and the New Zealanders, being more prevalent in the populations more influenced by Western lifestyle (Fig. 2).⁴ The author suggested that the increase in refined carbohydrate and decrease in dietary fibre intake was the factor of “Westernisation” responsible for this trend in the South Pacific islanders.^{4 51}

Cleave postulated that the loaded caecum on the right, and colon on the left, drag on and cause compression of the iliac veins when constipated. The small increase in pressure, causing obstruction to the venous return from the legs over the years, leads to the development of varicose veins.⁴⁸

Burkitt agreed that constipation is the main cause of varicose veins and also other “Western” diseases such as haemorrhoids and deep vein thrombosis.^{49 52} However his theory was that the raised intra-abdominal pressure from straining at stool is transmitted down the veins of the legs, and over the years this leads to dilatation of the veins and non-apposition of the valve cusps, thus rendering the veins incompetent.

Diverticular disease is another Western disease often blamed on a constipating diet. Interestingly varicose veins have been shown to occur more frequently in patients with diverticular disease compared with controls suggesting a possible common cause for both diseases.¹⁹

Squatting.—Burkitt alleges that squatting to defecate provides a mechanical protective mechanism for the leg veins by helping to prevent the rise in intra-abdominal pressure being transmitted down the veins and that this protective mechanism is lost with the use in the West of raised toilet seats.⁵² However, in a population study in Brazil no significant difference was found in the prevalence of varicose veins between those who used pedestal water closets and those who squatted to defecate, after accounting for age.⁷ In one study in Tanzania, Richardson found that almost all (31/32) people with varicose veins who were questioned had always squatted to defecate, and concluded that this position did not guarantee protection against the development of the condition.⁵³

Chair-sitting.—Alexander suggested an alternative hypothesis.⁵⁴ He argued that the practice of chair sitting is a relatively recent Western phenomenon, while the traditional Africans sit on the ground. He suggested that sitting in a chair increases the hydrostatic pressure exerted on the veins of the legs and that this leads to dilatation of the veins. The increased circumference of the veins leads to increased tension in the wall which itself causes extra stress. The erect posture of chair sitting leads to pooling of the blood in the legs which increases the dilating component of the kinetic force. All these factors contribute to increased stress on the veins. The effect of these factors during childhood leads to a constantly higher stress producing veins of an increased calibre. Factors such as pregnancy, standing and tight clothes would then be important as accelerating factors on higher calibre veins.

Thus the factor of “Westernisation” in this case is the practice of sitting in a chair, a habit which is not adopted by primitive communities where the prevalence of varicose veins is apparently low. In a study of New Guinea villagers, Stanhope found that it was the men who suffered from varicose veins and only discovered one woman with the condition. He suggested that the variation in the sitting positions might be the cause of this sex difference—women sit cross legged on the ground while men “sit on low stools or logs, ... or squat ... or sit on benches with the legs dangling”.⁹ This finding would support the chair-sitting hypothesis.

Other factors.—An association has been found between varicose veins and heavy lifting,¹⁸ and inguinal herniae in males,¹⁵ again supporting the idea that raised intra-abdominal pressure plays a role in the development of varicose veins. Associations between late menarche, and a- and hypo-galactorrhoea and varicose veins was found by Arnoldi suggesting a hormonal role.³ Lake *et al.* found a significantly higher prevalence of arterial disease in males with varicose veins;⁵⁵ results from the Framingham Study suggested that both conditions have similar risk factors which may account for their co-existence.¹⁶

Pathogenesis

Several theories have been suggested for the pathogenesis of varicose veins,⁴⁰⁻⁵⁶ summarised as follows:

1. *Valvular hypothesis*

The primary defect is in the valves of the veins which are thought to fail sequentially from above the saphenofemoral junction downwards. Exposure to transient high pressures leads to incompetence of the saphenofemoral valves. Repetition of the process eventually results in dilatation and varicosity of the thin walled branches of the saphenous vein.⁴⁰

2. *Vein wall hypothesis*

The primary defect is a weakness of the wall of the vein which dilates rather than hypertrophies under pressure. Microscopic studies have shown that infiltration of collagen into the vein wall disturbs the muscle cell-collagen-elastic fibre balance and leads to loss of contractility of the vein and hence dilatation.⁵⁷

3. *A-V anastomosis hypothesis*

The primary defect is hypothesised to be multiple small arterio-venous anastomoses in the subcutaneous tissues which in turn become varicose under pressure.

In one study supporting this theory, a higher PO₂ was found in the blood taken from varicosities compared with blood from arm veins in the same patients.⁵⁸

4. *Communicating vein hypothesis*

This assumes that the primary defect is incompetence of the valves of the perforating veins

and that varicose veins are caused by high pressure orthograde flow causing dilatation.

There is no rigorous proof for any of the above theories but it is argued that the "valvular" and "vein wall" hypotheses describe the more probable mechanisms of pathogenesis of varicose veins, either singly or in combination.⁴⁰

Conclusion

Varicose vein is predominantly a condition of westernised society and the prevalence increase with age. The primary cause is still unknown. At present there is little conclusive evidence for a genetic predisposition and studies point to an environmental cause associated with Western living. Many risk factors have been implicated such as the number of pregnancies, prolonged standing, the practice of chair-sitting, diet and constipation, and factors leading to raised intra-abdominal pressure e.g. obesity, heavy lifting and tight undergarments. It is possible that these are only accelerating causes in those already susceptible to the condition. However, if an environmental cause can be proven, then the preventing of varicose veins and their sequelae becomes a more realistic proposition.

More epidemiological work needs to be done. Definition and methods of measurements need to be universally agreed and conditions of investigation need to be standardised before more useful studies can be carried out. The distinction between "disorder" and "disease" is necessary in order to create a realistic picture of the importance of the condition.

Recently developed methods of assessment such as Duplex scanning promise new opportunities for following the progression of venous disease and should offer additional insight into the natural history and aetiology of this common but little studied condition. Perhaps then prophylaxis treatment will be a possibility.

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Original Article

Edinburgh Vein Study: Methods and Response in a Survey of Venous Disease in the General Population

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ABSTRACT

Objective: To describe the methods required to conduct a large epidemiological study of venous disease in the general population, and the resulting response.

Design: Cross-sectional study.

Setting: University of Edinburgh.

Participants: Men and women aged 18–64 years, randomly selected from general practice registers.

Methods: Subjects were invited for the following procedures: questionnaire, height and weight measurement, classification of varices and chronic venous insufficiency, duplex measurement of duration of venous reflux and venous blood sampling. A questionnaire survey of non-responders was carried out.

Results of response: A total of 1566 subjects attended, a final response rate of 53.8%. The response rate increased with age. The distribution of ethnic origin and social class of attenders was similar to that of the general Edinburgh population. Study participants were generally older, from more affluent areas and more often female than non-responders ($p \leq 0.001$).

Conclusions: Large epidemiological studies of venous disease in the community are feasible but the level of response illustrates the importance of obtaining information on the disease status of non-responders.

Keywords: Duplex scanning; Epidemiology; Varicose veins; Venous incompetence

Introduction

Venous insufficiency is common in the Western world. It has been estimated that the prevalence of varicose veins in the Western adult population is approximately 10–15% for men and 20–25% for women [1]. In the Lothian and Forth Valley Leg Ulcer Study, the prevalence of active leg ulceration was 1.5 per thousand population [2] and studies have shown that between 57% and 80% of leg ulcer patients have demonstrable venous disease [3]. The cost is considerable in terms of both morbidity and finance, with approximately 2% of national healthcare resources being spent on venous diseases [4].

Despite this, there have been relatively few population-based epidemiological studies in this area. Many previous studies of venous disease have investigated samples of clinic patients or specific occupational groups, and comparison of the results is further hampered by a lack of uniform definitions and methods of measurement [5]. The situation may become easier in the future with the recent publication of guidelines for the classification of venous disorders, which describe venous disease according to clinical signs, aetiology, anatomical distribution and pathophysiological condition [6]. In addition, duplex scanning now provides a non-invasive method of measurement of venous incompetence which is acceptable for use in epidemiological studies, and gives a new dimension to the assessment of venous conditions.

The Edinburgh Vein Study is the first study in the UK to investigate early venous disease in the general population using duplex scanning to measure venous incompetence. The aims of the study were to determine the prevalence of venous insufficiency of the legs in the

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general population and to investigate associations with certain genetic and lifestyle factors. This paper presents the methods used and gives details of response rates in the study.

Methods

Study Design

The study design was a cross-sectional survey of a random sample of the general population of Edinburgh. The initial study population will be followed-up as a cohort.

Study Population

The target population comprised men and women aged 18–64 years of age resident in Edinburgh.

Sample Size

The total sample size of 1500 participants was estimated on the basis of the number required to give an adequate precision for prevalence, to detect a significant difference in prevalence between groups, and to enable a subsequent follow-up study to be conducted. A prevalence of 20% was assumed for venous insufficiency and incompetence, requiring 1500 subjects to give this prevalence a precision of $\pm 2\%$. In addition, with 1500 subjects, a difference in prevalence of 7% or greater could be detected between groups, e.g. 20% in females and 13% in males. If 50% of the cross-sectional study participants were followed-up and 10% developed the end-point of interest, then an odds ratio of 1.5 or more could be detected. These calculations assumed a 5% significance level with 90% power.

Sample Recruitment

Twelve general practices, distributed geographically and socioeconomically throughout the city of Edinburgh, had their computerized age–sex registers divided into 10-year age bands for each sex, and random sampling was carried out within each age–sex group. The general practitioners reviewed the randomly selected lists of patients and excluded any whom they considered it was inappropriate to approach (e.g. those with terminal illness or severe dementia). From the remaining names in each age–sex group, a smaller number was then randomly selected to be invited to participate.

Following publicity in the local media, a letter of invitation signed jointly by the study coordinator and the subject's general practitioner was sent to each selected participant, inviting them to attend a research clinic at the university for an examination of their legs. Travel expenses were offered and evening appointment times were available for those unable to attend during the day. A home visit was offered to those unable to attend the clinic because of disability, etc.

Attempts were made to contact non-responders by telephone, where numbers were available, on a minimum of three occasions. For those non-responders not reached by telephone, a second letter of invitation was sent. Subjects whose letters were either returned by the Post Office or who had moved from the area were counted as 'returns'. If a period of at least 1 month had elapsed after sending a second invitation and still no contact was made with subjects, they seemed 'unreachable'. For each subject classified as a 'return' or an 'unreachable', an invitation was sent to another randomly selected subject in the same age–sex group from the same practice, where sufficient names remained available in the relevant group. Only one cycle of such replacement invitations was performed for each practice.

On receipt of an affirmative reply, an appointment time, map, details of the examination and a questionnaire were sent. The week before their attendance, the subject was contacted by telephone or post to remind them of their appointment. Responders who did not attend their appointment were offered a further appointment, usually by telephone, up to a total of three appointments. Those who withdrew from the study or ultimately failed to attend after agreeing to participate were counted as 'withdrawals'.

Study Measurements

Clinical examinations were held at a research clinic at the University of Edinburgh on certain weekdays and evenings between May 1994 and April 1996. Two subjects were examined concurrently during each appointment period of 75 min by one or more members of the research team, which comprised a research nurse, a technician and a clinical research fellow. Following each subject's appointment, a report of the clinical findings was sent to their general practitioner. Those subjects wishing more information on varicose veins were offered an advice leaflet [7] and referred back to their general practitioner. Nineteen subjects had a 'home visit' appointment because of their inability to attend the university clinic for medical or social reasons. All study measurements were performed at the home visits, apart from a duplex scan. Local ethics committee approval was given for the study and informed consent was obtained from each study participant.

Questionnaire

A self-administered questionnaire was completed by the subjects and checked by a member of the study team at the appointment. Details were asked about current marital and occupational status. The occupation covering the longest period of the subject's life and of their most recent partner/spouse or father was documented. Using this information, social class was coded for both individuals according to the Standard Occupational Classification [8]. Information was also obtained on standing, sitting, walking and lifting at work, past

relevant medical history including details of any treatment for varicose veins, family history of venous disease, leg symptoms, smoking and bowel habit. A dietary fibre questionnaire (Tinuviel Software, Warrington, UK) adapted from a validated Medical Research Council (MRC) fibre questionnaire [9] was completed, and an obstetric history was obtained for female subjects. In addition, the researcher documented the subject's ethnic origin as one of the following: White Caucasian, African, Indian, Chinese or other (to be specified).

Height and Weight

Subjects had their standing height measured once to the nearest 5 mm without shoes, using a free-standing metal ruler on a heavy base. Weight, without shoes or outer clothes, was measured to the nearest 100 g on a digital Soehnle scale. The height-measuring stick and weighing scales used throughout the study were periodically calibrated against another instrument.

Leg Examination and Photographs

The method of examination and classification of venous disease used in the Edinburgh Vein Study was adapted from the Basle Study [10]. During inspection of the legs, subjects stood on a raised platform with their feet in three standard positions: facing towards the examiner with heels together and forefeet spread apart, facing away from the examiner in a similar position, and facing away from the examiner with feet parallel (Fig. 1). They were asked to remain in a standing position for a minimum of 2 min before classification of their veins, to

allow the blood to pool in the legs. Any scars and notable findings on the legs were documented.

Varices were divided into three types as shown in Table 1: trunk varices, reticular varices, and hyphenweb varices. Each of the three groups was subdivided into grades of severity 1–3, determined according to the 'degree and extent of tortuosity and prominence of the veins' [10]. An additional category called 'perforators' (soft lumps that reduced on pressure and disappeared on elevation of the leg) was included to allow the documentation of visible incompetent perforating veins or blow-outs. This was thought to be desirable, particularly in the absence of any trunk varices. Each subject was also assessed for chronic venous insufficiency graded 1–3 as described in Table 1, and examined for the presence of any pitting ankle oedema.

As in the Basle Study [10], photographs of the legs were taken. Three standard photographs were taken with the subject in the examination positions described above: two facing away from and one facing towards the camera (Fig. 1). Any varicose vein operation scars were then marked with water-soluble ink, and further photographs were taken to document these. A Nikon FM2 camera with a 50 mm lens, flash, tripod and Ektachrome 200 colour slide film was used and positioned at a distance to allow visualization of the leg from the foot to mid/upper thigh. The photographic slides were subsequently analysed independently by the two members of the study team who had not examined the subject in the clinic, according to the classification system described above. If the classifications of the two observers viewing the slides differed by less than two grades in each category, discussion between these two

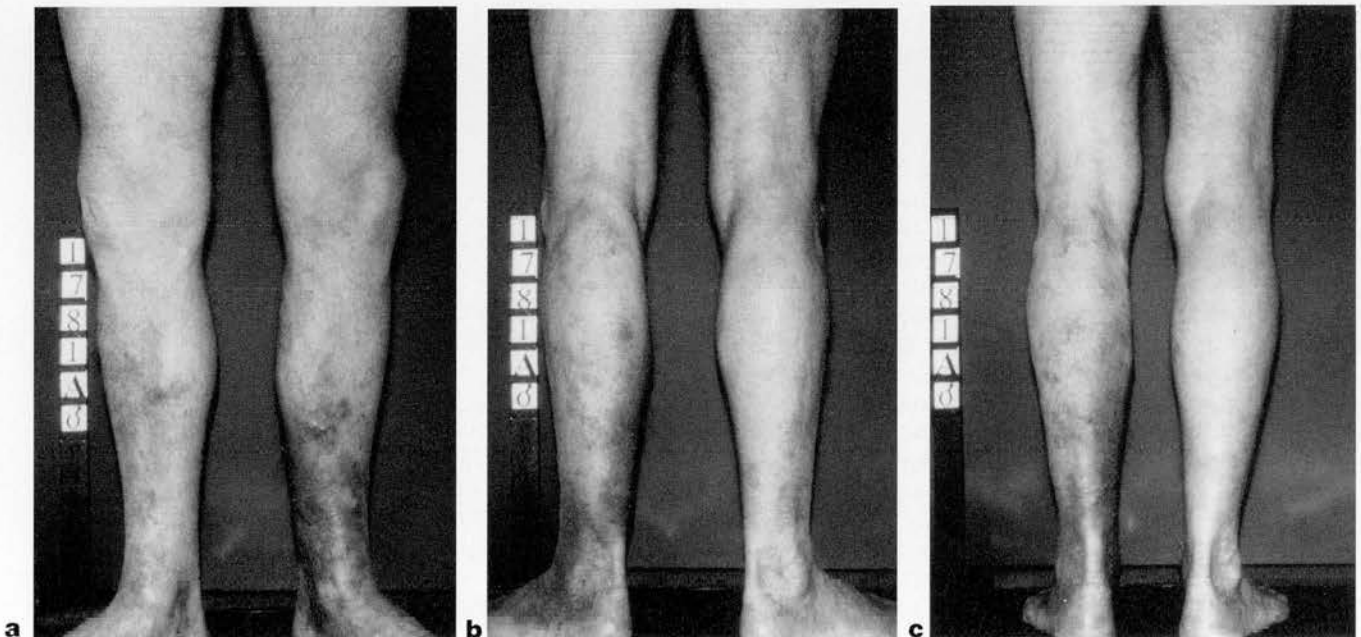


Fig. 1. Positions for examining the legs of subjects in the Edinburgh Vein Study. Subjects stood on an elevated stand. Legs were examined and photographs taken in three standardized positions: **a** facing towards examiner with heels together and forefeet spread apart; **b** facing away from the examiner with heels together and forefeet spread apart; and **c** facing away from the examiner with feet parallel.

Table 1. Classification used for examination of the legs in the Edinburgh Vein Study (adapted from Widmer [10])

Category	Definition	Grading
<i>Varices</i>		
Trunks	Dilated, tortuous trunks of the saphenous magna or parva vein and their branches of the first or second order	Grade 1–3 ^a
Reticulars	Dilated, tortuous subcutaneous veins not belonging to the main trunk or its major branches	Grade 1–3 ^a
Hyphenwebs	Intradermal varices	Grade 1–3 ^a
Perforators	Soft lumps that reduce on pressure and disappear on elevation of the leg	Absent/present
Chronic venous insufficiency	Dilated subcutaneous veins, 'corona phlebectatica' Hyper- or depigmented areas, with or without 'corona phlebectatica' Open or healed ulcer cruris	Grade 1 Grade 2 Grade 3

^aGrade of varices dependent on degree and extent of tortuosity and prominence of the veins.

observers achieved a consensus classification for each subject. If there was a difference of two or more grades in any one category, then an expert (C.V.R.) made the final decision. This process resulted in two independent classifications of the venous status of each subject: one based on examination in the clinic, and the other on analysis of the photographic slides.

Several measures were adopted before and during the study to limit observer variability. The research nurse and technician, who were the principal observers, were trained together initially in the method of classification of varices and chronic venous insufficiency. The photographic slides of subjects' legs were analysed and discussed weekly throughout the study by all three members of the research team and reference photographs were reviewed periodically as a reminder of the original standard.

Duplex Scanning

The duplex scans were performed with a Dasonics Prisma VST duplex scanner (Dasonics Sonotron, Zug, Switzerland) using a 5.0 MHz linear array probe. Cephalad venous flow was induced using a pneumatic cuff placed around the calf (cuff width 10 cm, length 50 cm), which was rapidly inflated and deflated using an automatic cuff inflator (Oak Medical, Scunthorpe, UK) to mimic a hand squeeze. For those calves of a larger diameter, a longer cuff was used (cuff width 10 cm, length 65 cm). A pressure of approximately 110 mmHg was used to inflate the cuffs. If this standard pressure did not produce a forward flow equivalent to a minimum standard Doppler shift of 0.5–1.0 kHz in the vein segment under examination, then a manual squeeze of the calf was used to elicit augmentation of venous flow for examination of that vein segment. Occasionally a manual squeeze of the thigh was employed. The refill time between compressions was a minimum of approximately 5 s.

Each subject was examined on a tilting couch (Akron Therapy Ltd, Ipswich, UK) and an angle of 45°. This position was chosen to give subjects some support in an attempt to minimize fainting during the procedure, while allowing the force of gravity to act on the leg. Any subjects who did feel faint at this angle had the examination performed at a lesser angle, in the 30°

head-up position. For examination of the thigh, subjects stood with their back to the couch with the leg to be examined everted and slightly bent at the knee, and the weight mainly on the opposite leg. For examination of the segments behind the knee, subjects stood facing the couch, with the leg to be examined slightly bent at the knee and the weight mainly on the opposite leg.

Measurements were made at the following eight points along the deep and superficial veins of both legs: the common femoral vein proximal to the sapheno-femoral junction; the superficial femoral vein (a) approximately 2 cm distal to the confluence with the profunda femoris vein and (b) in the lower third of the thigh; the popliteal vein (a) above and (b) below the knee crease; the long saphenous vein (a) just distal to the sapheno-femoral junction and (b) in the lower third of the thigh; and the short saphenous vein just distal to the sapheno-popliteal junction. In addition, the presence of any dual superficial femoral veins was documented and measurement of reflux in these veins performed.

When cephalad venous flow was induced in the limb under examination, any reflux present was identified on the Doppler spectrum. Two typical spectra were selected at each site and the duration of reflux was measured by placing the cursors at the beginning and end of the period of reflux. Time was calculated to the nearest hundredth of a second, to a maximum of 8 s, this being limited by the size of the screen. Duration of reflux greater than 8 s was recorded as 8.00 s. Presence of any turbulent flow was recorded when it led to difficulty in measuring accurately the duration of reflux. The mean of the two readings at each point on the vein was used in all subsequent analysis. Where there was a technical difficulty or query over part of the duplex scan, the subject was invited to return to have that part of the scan repeated by a radiologist (P.L.A.) with an Ultramark 9 HDI colour-flow duplex scanner (Advanced Technology Laboratories, Bothell, Washington). Where the measurements from these two scans differed significantly, the results of the second scan were used in the analysis. Periodically during the study, as a method of quality control, sequential duplex scans were performed by all three research team members on the same volunteers to allow interobserver comparison of results and identification and discussion of any problems.

Blood Sampling

With the patient in the recumbent position, 20 ml of venous blood was taken from the antecubital fossa with a 21G butterfly or needle. Ten millilitres was placed in an EDTA tube for subsequent extraction of DNA and future genetic analysis; 9 ml was placed in a tube with 1 ml 3.3% trisodium citrate, centrifuged for 20 min at 3000 Hz and then the plasma was pipetted off into 4 × 1 ml aliquots. These aliquots and the remaining red cells were stored at -40°C within 2 h of the blood sample being taken. The plasma was subsequently analysed for fibrinogen, D-dimer, von Willebrand factor and tissue plasminogen activator, and fatty acids were analysed in the phospholipid fraction of the red blood cells. During outlying home visits, blood samples were stored on ice for the journey back to the laboratory, prior to processing and freezing. As a quality control measure, twice the amount of blood was taken on a small number of subjects and sent to the laboratories in two batches with separate identifiers. Comparison of results of the matched samples allowed assessment of repeatability of the analysis techniques.

Bowel Record Form

Following attendance at an appointment, each subject was requested to complete a bowel record form, which documented the date and time of three consecutive stools. The subject was also asked to assign a number from 1 to 6 to each stool, based on the shape and consistency, and to say whether they strained at the start and finish of each stool. The average number of defecations per week was obtained from responses to questions in the general questionnaire and, with the information from the bowel record form, the subject's intestinal transit time was estimated according to the method described by Probert et al. [11].

Follow-up of Non-responders

Non-responders' Questionnaires

In this report, the term 'non-responders' will be used to describe those subjects who initially agree to participate in the study and subsequently withdrew or failed to attend their appointment ('withdrawals'), and those subjects who declined to participate in the study from the beginning ('refusals'). A survey was carried out of the non-responders from four of the 12 practices, using a one-page questionnaire to inquire about venous disease and any previous treatment for varicose veins.

Telephone Information

Additional information about self-reported varicose veins was sought from subjects from all practices who were contacted by telephone but declined to participate in the study.

Analysis of Results

Information from the recording forms and questionnaires was entered onto a DBASE IV database. Before analysis, all the examination and questionnaire data were entered by a different person a second time. Comparison of the two databases was performed to identify discrepancies, which were checked and corrected. The data files were transferred to the Edinburgh University Mainframe computer for analysis using the SPSS-X and SAS statistical packages. In analysis of the results of response, the following statistical tests were used: χ^2 -test for categorical data, Student's *t*-test for continuous parametric data and the Mann-Whitney test for continuous non-parametric data.

Results of Response

Response Rate

A total of 5250 names was extracted from the computerized age-sex registers of the 12 participating general practices. The general practitioners excluded 343 names because they were considered unsuitable to be approached or because they had moved away from the practice. Of the 4103 invitations that were sent, 618 subjects had moved away ('returns') and 573 subjects were uncontactable ('unreachables'). A further 998 subjects indicated that they did not wish to take part in the study ('refusals'). The number who agreed to participate was 1914. However, 348 of these subjects subsequently withdrew or did not attend their appointment ('withdrawals'), resulting in a study population of 1566 subjects. Of those people contacted who were still living in the area and hence eligible to participate, the final response rate was 53.8%.

Age and Sex

Equal numbers of men and women were invited to participate in the study; 21.3% of the initial invitations were sent to subjects in each of the four 10-year age bands and 14.9% to subjects in the youngest 7-year age band. The final response rate according to age band and sex is illustrated in Table 2. The response rate was 56.9% for females and 50.4% for males and increased with age from 34.3% in the 18-24 years olds to 61.3% in the 55-64 year olds.

Of the study participants, 867 (55.4%) were female and 699 (44.6%) were male. There was no significant difference between the mean age of the females and males who participated (44.78 years versus 45.85 years, $p > 0.05$). The attenders were older and contained a higher proportion of females than the non-responders (55.4% versus 48.8%; both $p \leq 0.001$).

Table 3 compares the age and sex distribution of the Edinburgh Vein Study attenders with the population of Edinburgh aged 18-64 years, according to the 1991

Table 2. Response rate in Edinburgh Vein Study according to age and sex

	Age (years)											
	18–24		25–34		35–44		45–54		55–64		Total	
	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)
Males	30.2	(55)	41.4	(103)	55.1	(158)	55.4	(181)	58.9	(202)	50.4	(699)
Females	38.0	(76)	52.7	(158)	55.4	(186)	66.2	(227)	63.8	(220)	56.9	(867)
Total	34.3	(131)	47.5	(261)	55.2	(344)	60.9	(408)	61.3	(422)	53.8	(1566)

n, Number of attenders in each group.

Table 3. Comparison of age range and sex of Edinburgh Vein Study attenders with City of Edinburgh population aged 18–64 years [12]

Age (years)	Males (%)		Females (%)		Total (%)	
	Edinburgh Vein Study (n=699)	City of Edinburgh (n=129 641)	Edinburgh Vein Study (n=867)	City of Edinburgh (n=138 014)	Edinburgh Vein Study (n=1566)	City of Edinburgh (n=267 655)
18–24	7.9	17.3	8.8	17.4	8.4	17.4
25–34	14.7	27.4	18.2	27.0	16.7	27.2
35–44	22.6	22.1	21.5	21.2	22.0	21.6
45–54	25.9	17.0	26.2	17.1	26.1	17.1
55–64	28.9	16.1	25.4	17.3	26.9	16.7

census figures [12]. The Edinburgh Vein Study population contained proportionally more older people (45–64 years) and fewer younger people (18–34 years) than the population of Edinburgh as a whole. Of the study population, 16.7% were in the 25–34 year age group and 26.9% in the 55–64 year age group, compared with 27.2% and 16.7%, respectively, in the Edinburgh population. Women accounted for 55.4% of the Edinburgh Vein Study population, compared with 51.6% of the Edinburgh population aged 18–64 years.

In summary, more women than men and more older than younger people attended the Edinburgh Vein Study. The resulting study population contained a higher proportion of older people and a slightly higher proportion of women when compared with the population of Edinburgh in the same age range.

Ethnic Origin

Of the 1566 attenders, 1548 (98.9%) were White Caucasian, seven (0.4%) were Chinese, and three (0.2%) each were African and Indian. Of the five (0.3%) in the 'other' group, three were Iranian, one was Korean and one was Central American/White Caucasian. The 1991 Census figures showed that 97.7% of the City of Edinburgh population in the 18–64 year age group were White Caucasian. The ethnic minorities with the highest representation were Pakistanis, comprising 0.6% of this age group, and Chinese, accounting for 0.5% [12].

Social Class

Two analyses of social class and response were made: (a) between the study attenders and the City of

Edinburgh population and (b) between the study attenders and non-responders.

Comparison of Attenders with Edinburgh Population

Figure 2 compares the social class distribution of the 'economically active' people in the Edinburgh Vein Study population with the figures for the 10% sample of the City of Edinburgh population aged 16 years and over, obtained from the 1991 Census [13]. Similar patterns exist between the two population samples. Most people were in social classes II or IIIN in both the Edinburgh Vein Study population (37.0% and 24.8%) and the City of Edinburgh population (30.4% and 26.3%). Both populations followed the same decreasing trend from social class II through to social class V. The Edinburgh Vein Study population had slightly lower proportions in social classes IV and V than the City of Edinburgh population (7.1% and 4.4% versus 11.3% and 6.3%, respectively) and a higher proportion in social class I (10.8% versus 8.5%). After reclassifying 'economically active' students from the 1991 Census as 'economically inactive' to be comparable with the Edinburgh Vein Study classification [12,15] (see Fig. 2 caption), 76.9% of the City of Edinburgh population aged 18–64 years were 'economically active' compared with 78.0% of the Edinburgh Vein Study population.

Comparison of Attenders with Non-responders

In order to compare social status of attenders in the study with the non-responders, for whom no occupational data were available, the Carstairs score for deprivation was used [16]. This score is based on the subject's postcode sector and allows quantification of relative deprivation or affluence in different localities [17]. The information

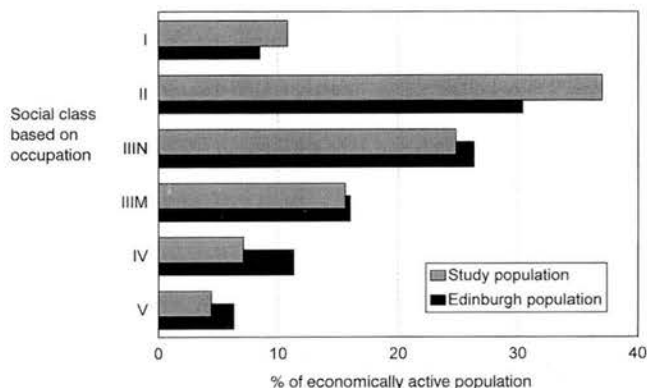


Fig. 2. Comparison of the social class of 'economically active' persons in the Edinburgh Vein Study population with a 10% sample of the City of Edinburgh population aged 16 years and over [13]. To be comparable with the 1991 Census definitions of 'economically active persons', the following groups from the Edinburgh Vein Study population were regarded as 'economically inactive' and excluded from the figures for social class: retired subjects, housewives and students (current and those who were in these groups for the longest period of their lives). Those in the armed forces were classified as economically active but not assigned a social class. Also excluded from the social class figures were those who were currently unemployed and who (a) in their Edinburgh Vein Study questionnaire gave no previous job details or who (b) in the Census stated that they had no job during the previous 10 years [14]. However, two discrepancies between the groups remained. In the Census, students were assigned a social class if they had had a job during the past 10 years [15]. In the Edinburgh Vein Study, no students were assigned a social class. Finally, there was a separate classification in the Census for those 'on a government scheme'. They were regarded as 'economically active' but were not assigned a social class, and were therefore excluded here from the social class figures [15]. They were, however, included in the total figures for economic activity (see text). There was no such classification in the Edinburgh Vein Study and these people would have been classified in the most appropriate available category.

used to calculate the 1991 scores was derived from the Small Area Statistics Tables of the 1991 Census. The all-Scotland mean deprivation score is zero: the more negative the score, the more relatively affluent the postcode sector; the more positive the score, the more relatively deprived the postcode sector. In addition, the distribution of deprivation scores is restructured into a categorical variable called DEPCAT, ranging from DEPCAT 1 (most affluent postcode sectors) to DEPCAT 7 (most deprived postcode sectors) [17]. Both the deprivation categories and deprivation scores

were used in the comparison of the attenders and non-responders in the Edinburgh Vein Study.

Of the 4103 subjects invited to participate in the Edinburgh Vein Study, postcodes were missing for 259 subjects, including 118 attenders and 94 non-responders. Deprivation scores were calculated for all the others. Table 4 shows the deprivation categories (DEPCAT 1–7) of the attenders, compared with the total group who were contacted and eligible to participate in the Edinburgh Vein Study. The attenders had a slightly higher proportion of their subjects in the more affluent deprivation categories 1–3 (56.1%) compared with the total group contacted (51.5%), and a correspondingly smaller proportion in the more deprived categories 4–7. The deprivation scores (DEPScore) for all those contacted and eligible to participate were skewed towards the more affluent categories. The median deprivation score for the attenders (-1.34 , interquartile range -3.66 to $+1.14$) was significantly lower (more affluent) than that of the non-responders (-0.34 , interquartile range -2.18 to $+1.89$) ($p \leq 0.001$).

In summary, the attenders at the Edinburgh Vein Study were from relatively more affluent areas than the non-responders. When assessed according to occupation, the overall social class distribution of the study population followed a similar pattern to the general population of Edinburgh age 16 years and over, although a higher proportion of the study attenders were in social classes I and II.

Discussion

The Edinburgh Vein Study will provide new information on the epidemiology of venous disease in the general population. The relatively young age range of the population was selected in order to allow the investigation of early venous disease and to follow through the natural history of venous insufficiency in the cohort from an early stage. Although other classifications of chronic venous insufficiency were available at the time of planning the study [18], Widmer's classification of venous disease was used because it was considered to provide the most detailed classification available for the different degrees of varicose veins [1]. In addition, the use of colour photographic slides will provide a

Table 4. Comparison of deprivation categories (DEPCAT) [17] of study attenders with all those contacted and eligible to participate in the Edinburgh Vein Study

	Subjects with postcodes (total)	% in each DEPCAT						
		1	2	3	4	5	6	7
Attenders	1448 (1566)	15.7	12.9	27.5	16.7	15.7	4.1	7.3
Whole group ^a	2700 (2912)	13.3	11.9	26.3	17.5	16.0	4.6	10.5

^a'Whole group' comprises all those subjects who were contacted and eligible to participate (i.e. attenders and non-responders).

permanent record of venous status at baseline for use in follow-up studies.

This study will provide new information on the prevalence of venous incompetence in the general population, and help to clarify further the relationship between venous incompetence at different anatomical sites and the clinical manifestations of venous insufficiency. Measurement of duration of reflux in individual vein segments has become an accepted method of assessing the presence of venous incompetence, although a recent study has shown that the method should not be used to quantify the degree of reflux [19]. The method used in the Edinburgh Vein Study follows work on the assessment of repeatability of duplex scanning for use in such studies [20].

Among the various theories of causation of varicose veins, there is a postulated link between a low-fibre diet, constipation and varices [21,22] although the evidence to support these theories is lacking [1]. The Edinburgh Vein Study will provide data on dietary fibre intake and on intestinal transit time, to allow a more objective analysis of the association between fibre in the diet, bowel habit and venous insufficiency than has been previously possible.

This study illustrates some of the problems of carrying out a survey on a general population sample, particularly the difficulty in recruiting a young, mobile, working population to investigate a condition that has a low profile and is not life-threatening. One alternative would have been to investigate venous disease in a specific population or occupational group where a more 'captive' target population would have been likely to yield a much higher response rate. However, much would have been lost in such an approach because the final results would have limited application to the general population. Furthermore, in the Edinburgh Vein Study, a concerted effort was made to obtain a representative sample of the city's population by involving participation from general practices situated in the most deprived areas of the city and not simply those in more affluent areas where the response rate would have been higher.

The final response rate was calculated by excluding from the target population number all those subjects identified during the study as having moved from the area ('returns'), and all those subjects who were not contacted despite repeated efforts to do so ('unreachables'). It could be argued that some of these 'unreachables' may have received their invitation to participate in the study but chose not to reply, in which case they should be classed as non-responders and not excluded from calculation of the response rate. In a previous study which sent questionnaires to a random sample of 18-75 year olds selected from a general practice register in Stockport, it was shown that 22% of patients were unlikely to have received their mailed questionnaire as they were not living at the address on the register [23]. If 22% of the Edinburgh Vein Study population had failed to receive their invitation and were therefore excluded from the calculation, the response rate would have been approximately 47.7%. Although it

is difficult to define the precise figure, the true response rate of those contacted and living in the area must lie between 44.9% (the figure obtained if all of the 'unreachables' received their invitation) and 53.8% (if none of the 'unreachables' received their invitation).

An important issue in a study of this kind is the way in which the attenders differed from the non-responders. In the Edinburgh Vein Study the attenders were generally older than the non-responders and from relatively more affluent areas. The matter really at issue, however, is how the groups differed with respect to venous disease. The follow-up performed of the non-responders will enable the effect of any non-response bias to be evaluated and the prevalence of venous disease in the whole population to be estimated.

In summary, as the first study of its kind in the UK, the Edinburgh Vein Study will provide information on the prevalence of varicose veins and chronic venous insufficiency in the general population and on associated risk factors. Measurement of underlying venous incompetence by duplex scanning will provide a more objective assessment of the venous status of the study population and additional information on the relationship between venous incompetence at various sites in the lower limb and the clinical manifestations of venous disease.

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Prevalence of venous reflux in the general population on duplex scanning: The Edinburgh Vein Study

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Purpose: The prevalence of reflux in the deep and superficial venous systems in the Edinburgh population and the relationship between patterns of reflux and the presence of venous disease on clinical examination were studied.

Methods: A cross-sectional survey was done on men and women ranging in age from 18 to 64 years, randomly selected from 12 general practices. The presence of varicose veins and chronic venous insufficiency was noted on clinical examination, as was the duration of venous reflux by means of duplex scanning in 8 vein segments on each leg. Results were compared using cut-off points for reflux duration (RD) of 0.5 seconds or more ($RD \geq 0.5$) and more than 1.0 second ($RD > 1.0$) to define reflux.

Results: There were 1566 study participants, 867 women and 699 men. The prevalence of reflux was similar in the right and left legs. The proportion of participants with reflux was highest in the lower thigh long saphenous vein (LSV) segment (18.6% in the right leg and 17.5% in the left leg for $RD \geq 0.5$), followed by the above knee popliteal segments (12.3% in the right leg and 11.0% in the left leg for $RD \geq 0.5$), the below knee popliteal (11.3% in the right leg and 9.5% in the left leg for $RD \geq 0.5$), upper LSV (10.0% in the right leg and 10.8% in the left leg for $RD \geq 0.5$) segments, the common femoral vein segments (7.8% in the right leg and 8.0% in the left leg for $RD \geq 0.5$), the lower superficial femoral vein (SFV) segments (6.6% in the right leg and 6.4% in the left leg for $RD \geq 0.5$), and the upper SFV (5.2% in the right leg and 4.7% in the left leg for $RD \geq 0.5$) and short saphenous vein (SSV) (4.6% in the right leg and 5.6% in the left leg for an $RD \geq 0.5$) segments. In the superficial vein segments, there was little difference in the occurrence of reflux whether $RD \geq 0.5$ or $RD > 1.0$ was used; but in the different deep vein segments, the prevalence of reflux was 2 to 4 times greater for $RD \geq 0.5$ rather than $RD > 1.0$. Men had a higher prevalence of reflux in the deep vein segments than women, reaching statistical significance ($P \leq .01$) in 4 of 5 segments for $RD \geq 0.5$. In general, the prevalence of reflux increased with age. Those with "venous disease" had a significantly higher prevalence of reflux in all vein segments than those with "no disease" ($P \leq .001$).

Conclusion: The prevalence of venous reflux in the general population was related to the presence of "venous disease," although it was also present in those without clinically apparent disease. There was a higher prevalence of reflux in the deep veins in men than the deep veins in women. Follow-up study of the population will determine the extent to which reflux is a predictor of future disease and complications. (*J Vasc Surg* 1998;28:767-76.)

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Duplex scanning has become the method of choice for the investigation of venous reflux.¹ It combines the assessment of anatomic structure and the functional evaluation of blood flow² to enable quantification of reflux duration in specific superficial and deep vein segments.¹ In addition, as a non-invasive and repeatable method of measurement, it is suitable for use in epidemiological studies.

Studies correlating reflux findings on duplex scanning with various stages of venous disease have increased knowledge of the patterns of reflux in venous patients.³⁻⁶ In addition, the reflux patterns in apparently healthy volunteers were described in one small study.⁷ In the Bochum Study, the venous Doppler and clinical findings on the lower limbs of a cohort of German schoolchildren were reported.⁸ However, to our knowledge, no previous study has investigated the distribution of venous reflux on duplex scanning in a large random sample of the adult population.

The Edinburgh Vein Study was the first study in the United Kingdom to investigate venous disease in the general population, using duplex scanning as a means of measuring venous reflux. The prevalence of varicose veins and chronic venous insufficiency of the legs in the general population and the associations with a range of genetic and lifestyle factors were studied. We sought to determine the prevalence of reflux in the deep and superficial venous systems in the general population and to relate the patterns of reflux to the overall presence of clinical venous disease.

PARTICIPANTS AND METHODS

The Edinburgh Vein Study is a cross-sectional survey, with a target population comprising men and women aged 18 to 64 years who live in Edinburgh. An age-stratified random sample was selected from the computerized age-sex registers of 12 general practices, which served areas geographically and socioeconomically distributed throughout the city. A sample size of 1500 participants was estimated, based on the number required to give an adequate precision for prevalence, to detect a significant difference in prevalence between groups, and to enable a subsequent follow-up study to be conducted. Details of the methods and response in the Edinburgh Vein Study have been reported.⁹

Participants went to a clinic at the University of Edinburgh between May 1994 and April 1996 and were examined by 1 or more members of a research team, comprising a nurse, technician, and clinical research fellow. Participants completed a

self-administered questionnaire that included personal and occupational details, relevant medical and family history, and possible risk factors for venous disease. The height of each participant without shoes was measured to the nearest 5 mm, using a free-standing metal ruler on a heavy base. Weight, without shoes or outer clothes, was measured to the nearest 100 g on a digital Soehnle scale.

The method of examination and classification of venous disease was adapted from the Basle Study.¹⁰ (The CEAP classification for chronic venous disease, published in 1995,¹ was not available at the time of design and start of recruitment in the Edinburgh Vein Study. The Basle Study classification was considered to be the best available classification of venous disease at the time,¹¹ providing the best detail for the different degrees of varicose veins.) Participants stood on a raised platform with their feet in 3 standard positions and were asked to remain in a standing position for a minimum of 2 minutes to allow the blood to pool in the legs before classification of their veins. Varices were divided into 3 types: trunk varices (dilated, tortuous trunks of the saphena magna or parva vein and their branches of the first or second order), reticular varices (dilated, tortuous subcutaneous veins not belonging to the main trunk or its major branches), and hyphenweb varices (intradermal varices). Each of the 3 groups was subdivided into grades of severity from 1 to 3, determined according to the "degree and extent of tortuosity and prominence of the veins."¹⁰ An additional category called "perforators" (soft lumps that reduced on pressure and disappeared on elevation of the leg) was included to allow the documentation of possible incompetent perforating veins or blowouts. The lack of sensitivity and specificity of this definition of perforators was recognized. However, such abnormalities were documented to avoid subsequent misclassification of participants with no trunk varices when grouping the study population into those with "venous disease" and those with "no disease" (see below). Each participant was also examined for the presence of any pitting ankle oedema and assessed for chronic venous insufficiency (CVI) graded 1 to 3. Grade 1 CVI was "corona phlebectatica/dilated subcutaneous veins;" grade 2 was "hyper- or de-pigmented areas with or without corona phlebectatica;" and grade 3 was "open or healed ulcer cruris."¹⁰ (The grades of CVI correspond to the CEAP clinical classification for chronic venous disease¹ as follows: grade 1 CVI corresponds to class 1 [malleolar flare]; grade 2 CVI corresponds to class 4 [skin changes]; and grade 3 CVI corre-

sponds to classes 5 and 6 [healed or active ulceration].) For the purposes of this report, participants were divided according to venous disease status: the group with "no disease" comprised those participants with no trunk varices, CVI, perforators, or history of varicose vein treatment and a maximum of grade 1 hyphenweb and/or reticular varices; the group with "venous disease" included all participants with trunk varices and/or CVI.

The duplex scans were performed with a Dasonics Prisma VST duplex scanner (Dasonics Sonotron, Zug, Switzerland) with a 5.0 MHz linear array probe. Cephalad venous flow was induced by means of a pneumatic cuff placed around the calf (cuff width, 10 cm; length 50 cm), which was rapidly inflated and deflated using an automatic cuff inflator (Oak Medical, Scunthorpe, United Kingdom) to mimic a hand squeeze. For those calves of a larger diameter, a longer cuff was used (cuff width, 10 cm; length, 65 cm). A pressure of approximately 110 mm Hg was used to inflate the cuffs. If this standard pressure did not produce a forward flow equivalent to a minimum standard Doppler shift of 0.5 to 1.0 kHz in the vein segment under examination, then a manual squeeze of the calf was used to elicit augmentation of venous flow for examination of that vein segment. Occasionally, a manual squeeze of the thigh was used. The refill time between compressions was a minimum of approximately 5 seconds.

Each participant was examined on a tilting couch (Akron Therapy Products, Ipswich, United Kingdom) at a 45° angle. A pilot study conducted before the Edinburgh Vein Study reported that a significant number of young participants felt faint while standing on a tilting couch in the near upright position during duplex examination. Therefore, the 45° position was chosen to give participants some support, and to minimize fainting during the procedure while allowing gravity to act on blood within the leg. Any participant who felt faint at this angle was examined in the 30° head-up position. For examination of the thigh, participants stood with their backs to the couch, with the leg to be examined everted and slightly bent at the knee and the weight mainly on the opposite leg. When the segments behind the knee were examined, participants stood facing the couch, with the leg to be examined slightly bent at the knee and the weight mainly on the opposite leg.

Measurements were made in 8 vein segments along the deep and superficial veins of both legs: (1) the common femoral vein (CFV) proximal to the sapheno-femoral junction; (2) the superficial femoral vein approximately 2 cm distal to the confluence with

the profunda femoris vein (upper SFV); (3) the superficial femoral vein in the lower third of the thigh (lower SFV); (4) the popliteal vein above the knee crease (above knee popliteal); (5) the popliteal vein below the knee crease (below knee popliteal); (6) the long saphenous vein just distal to the sapheno-femoral junction (upper LSV); (7) the long saphenous vein in the lower third of the thigh (lower thigh LSV); and (8) the short saphenous vein just distal to the sapheno-popliteal junction (SSV). In addition, the presence of any dual superficial femoral veins was documented, and the duration of reflux in these veins was measured.

When cephalad venous flow was induced in the limb under examination, any reflux present was identified on the Doppler spectrum. Two typical spectra were selected at each site, and the duration of reflux was measured by placing the cursors at the beginning and end of the period of reflux. Time was calculated to the nearest hundredth of a second, to a maximum of 8 seconds as limited by the size of the screen. Reflux duration (RD) greater than 8 seconds was recorded as 8.00 seconds. Presence of any turbulent flow was recorded when it led to difficulty in accurately measuring the RD. The mean of the 2 readings at each point on the vein was used in all subsequent analysis. When there was a technical difficulty or query about part of the duplex scan, the participant was asked to return to have that part of the scan repeated by a radiologist (P.L.A.), who used an Ultramark 9 HDI color-flow duplex scanner (Advanced Technology Laboratories, Bothell, Wash). When the measurements from these 2 scans differed significantly, the results of the second scan were used in the analysis.

All 3 research team members were involved for the duration of the study, and there were no changes in personnel. Several measures were adopted before and during the study to limit observer variability. The research nurse and technician, who were the principal observers, were trained together initially in the method of classification of varices and chronic venous insufficiency. The photographic slides of participants' legs were analyzed and discussed weekly by all 3 observers, and reference photographs were reviewed periodically as a reminder of the original standard. From time to time during the study, sequential duplex scans were performed by all 3 observers on the same volunteers to allow interobserver comparison of results and identification and discussion of any problems.

After each participant's appointment, a report of the clinical findings was sent to the participant's gen-

Table I. Prevalence of reflux of 0.5 seconds or more duration and reflux more than 1.0 second duration in individual vein segments, for legs separately and together

Vein segment	Right leg			Left leg			Both legs		
	Total (n)*	≥0.5 sec %	>1.0 sec %	Total (n)*	≥0.5 sec %	>1.0 sec %	Total (n)	≥0.5 sec %	>1.0 sec %
CFV	(1542)	7.8	2.1	(1539)	8.0	2.1	(1539)	2.5	0.6
Upper SFV	(1539)	5.2	1.2	(1540)	4.7	1.3	(1537)	1.7	0.3
Lower SFV	(1539)	6.6	2.5	(1538)	6.4	2.7	(1536)	2.2	0.8
Above knee popliteal	(1541)	12.3	5.0	(1541)	11.0	5.3	(1541)	3.9	1.3
Below knee popliteal	(1540)	11.3	4.7	(1541)	9.5	4.6	(1540)	3.3	1.0
Upper LSV	(1485)	10.0	9.6	(1477)	10.8	10.1	(1449)	4.8	4.6
Lower thigh LSV	(1422)	18.6	17.7	(1432)	17.5	16.7	(1363)	8.0	7.5
SSV	(1342)	4.6	3.7	(1351)	5.6	4.2	(1241)	1.6	1.1

*Missing values included: vein segment not visualized (eg, after vein stripping); absence of flow in vein segment; participants unable to undergo all or part of the scan because of a pre-existing medical condition, feeling faint, or the examination being performed in their home.

Reflux in "both legs" calculated as a percentage of those participants who had valid duplex measurements for that vein segment in both legs.

CFV, common femoral vein; SFV, superficial femoral vein; LSV, long saphenous vein; SSV, short saphenous vein.

eral practitioner. Those participants who wanted more information on varicose veins were offered a brochure and referred back to their general practitioners. "Home visit" appointments were made for 19 participants who were not able to go to the university clinic because of medical or social reasons. All study measurements, except the duplex scans, were performed during the home visits. Local ethics committee approval was given for the study, and informed consent was obtained from each study participant.

A survey of the "nonresponders" (ie, those who initially agreed to participate in the study but subsequently withdrew or failed to attend their appointments and those who declined to participate in the study from the beginning) was carried out in 4 of the 12 practices. This survey took the form of a 1-page questionnaire, which inquired about past history of venous disease and treatment for varicose veins.

Information from the recording forms and questionnaires was entered in a DBASE IV database. The data files were transferred to the Edinburgh University mainframe computer for analysis with the SPSS-X and SAS statistical packages. The following statistical tests were used: χ^2 test and Mantel-Haenszel test for linear association for categorical data, and Student *t* test for continuous parametric data. The age-adjusted percentages were calculated using a SAS macro (GLIMMIX), which fits generalized linear-mixed models. Results were compared with cut-off points for an RD of 0.5 seconds or more (RD \geq 0.5) and for an RD of more than 1.0 second (RD $>$ 1.0) to define reflux.

RESULTS

A total of 1566 participants, 867 women and 699 men, were examined. There were 1346 "nonresponders" (998 who refused to participate, and 348 who agreed to take part in the study but subsequently withdrew), resulting in a response rate of 53.8% of those contacted and still living in the area. The mean age of study participants was 44.8 years for women and 45.8 years for men. The age-adjusted prevalence of trunk varices was 39.7% in men and 32.2% in women ($P \leq .01$). Hyphenweb and reticular varices each affected more than 80% of participants, although most participants were affected to a mild degree only. The age-adjusted prevalence of chronic venous insufficiency was 9.4% in men and 6.6% in women ($P \leq .05$). In the survey of nonresponders, 6.5% of the 194 nonresponders who returned their questionnaire reported having received a doctor's diagnosis of varicose veins, compared with 13.3% of the study participants from the same practices who did respond ($P \leq .05$; figures adjusted for age and sex). Of the men, 6.7% of nonresponders and 9.1% of participants reported having received a doctor's diagnosis of varicose veins ($P > .05$), compared with 6.5% of female nonresponders and 16.7% of female participants ($P \leq .05$).¹² Table I shows the prevalence RD \geq 0.5 and the prevalence of RD $>$ 1.0 for each vein segment in right and left legs separately and in both legs together. (In addition, a dual superficial femoral vein was visualized in 471 participants in the right leg, in 458 participants in the left leg, and in 277 participants in both legs; however, in each leg only 2 participants [0.4%] showed RD \geq 0.5 in this vein.)

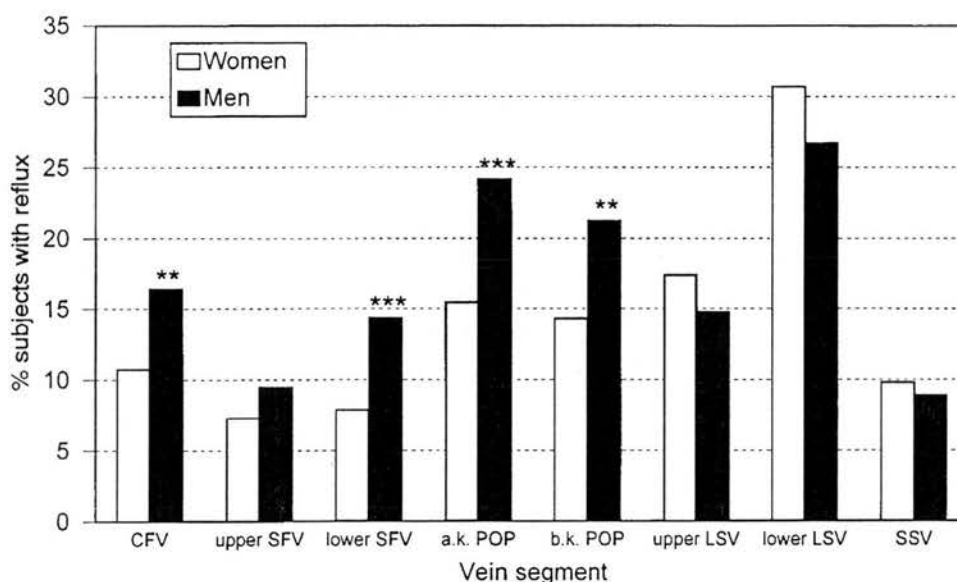


Fig 1. Proportion of participants with reflux of 0.5 seconds or more duration in either leg at individual vein segments, by sex (adjusted for age). CFV, common femoral vein; SFV, superficial femoral vein; a.k. POP, above knee popliteal; b.k. POP, below knee popliteal; LSV, long saphenous vein; lower LSV, lower thigh LSV; SSV, short saphenous vein.

There was little difference in the prevalence of reflux between the right and left legs for either $RD \geq 0.5$ or $RD > 1.0$. The lower thigh LSV segment most often showed reflux, compared with all other deep and superficial vein segments examined, with 18.6% of participants having an $RD \geq 0.5$ at this segment in the right leg, 17.5% in the left leg, and 8.0% in both legs. (Only 1241 of the 1566 participants had valid results for SSV segments in both legs. If a short saphenous vein could not be visualized or confidently identified as such, it was recorded as a missing value rather than assuming that there was no reflux present in the SSV.) Among the deep vein segments, the above knee popliteal segments most often showed reflux. In the superficial vein segments, there was little difference between the proportion of participants with $RD \geq 0.5$ and participants with $RD > 1.0$. However, in the different deep vein segments, the prevalence of $RD \geq 0.5$ was 2 to 4 times higher than the prevalence of $RD > 1.0$. The presence of turbulence was recorded in less than 2.5% of participants in each vein segment except the CFV segments, where it was documented in 8.0% of participants on the right leg and 9.8% of participants on the left leg.

Fig 1 compares the age-adjusted prevalence in men and women of $RD \geq 0.5$ in either leg at individual vein segments. For all deep vein segments, men had a higher prevalence of reflux than women. This sex difference reached statistical significance in

all deep vein segments except the upper SFV. Conversely, women had a higher prevalence of reflux in the superficial vein segments, although the sex differences in these segments were not statistically significant (all $P > .05$). If more women than men had their incompetent superficial veins surgically removed, resulting in missing values for some superficial vein segments, that would have led to a misleading reduction in this sex differential. Therefore, participants who had missing values for individual LSV segments on duplex scanning and who also reported having had previous varicose vein surgery were identified. Even assuming that all these participants would have had $RD \geq 0.5$ in the missing LSV segments, the sex differential for reflux in the upper and lower thigh LSV segments did not attain statistical significance ($P > .05$). For $RD > 1.0$, men continued to have a higher prevalence than women of reflux in the lower SFV ($P \leq .01$) and the below knee popliteal ($P \leq .05$) segments. However, for $RD > 1.0$, the sex differential for the above knee popliteal segment decreased ($P > .05$), and in the CFV and upper SFV segments, the proportions of men and women with $RD > 1.0$ were almost identical (CFV, 3.7% of men and 3.5% of women; upper SFV, 2.2% of men and 2.3% of women) (both $P > .05$). For $RD > 1.0$, women had a higher prevalence of reflux in their superficial vein segments than men, although, again, the sex differences were not significant.

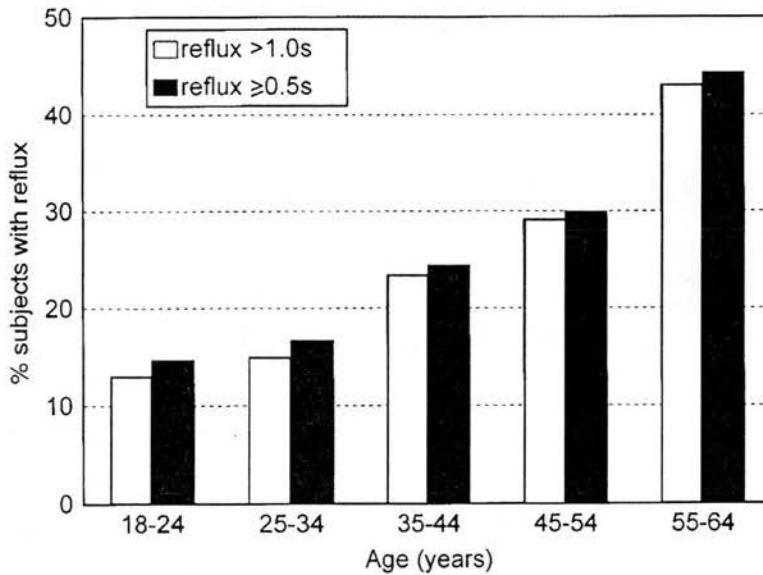


Fig 2. Proportion of participants with reflux of 0.5 seconds or more duration and reflux of more than 1.0 seconds duration in the lower thigh segment of the long saphenous vein in either leg, by age.

Table IIa. Patterns of reflux in the femoral and long saphenous veins

Vein segment	Right leg (n = 1483) % with reflux		Left leg (n = 1476) % with reflux	
	≥0.5 sec	>1.0 sec	≥0.5 sec	>1.0 sec
CFV (total)	7.4	2.0	7.5	2.0
CFV & upper LSV only	2.0	1.2	2.2	1.3
CFV & upper SFV only	1.1	0.1	0.9	0.1
CFV & upper SFV & upper LSV	0.5	0.3	0.5	0.3

(n), number of participants with complete duplex data for all relevant vein segments; CFV, common femoral vein; LSV, long saphenous vein; SFV, superficial femoral vein.

Table IIb. Patterns of reflux in the popliteal and short saphenous veins

Vein segment	Right leg (n = 1341) % with reflux		Left leg (n = 1351) % with reflux	
	≥0.5 sec	>1.0 sec	≥0.5 sec	>1.0 sec
Above knee popliteal (total)	12.5	5.0	11.0	5.3
Above knee popliteal & SSV only	1.0	0.6	0.8	0.5
Above & below knee popliteal only	5.7	1.9	5.0	2.4
Above & below knee popliteal & SSV	1.3	0.6	1.5	0.5

(n), number of participants with complete duplex data for all relevant vein segments; SSV, short saphenous vein.

In many of the vein segments, there was a trend toward a higher prevalence of reflux in the older age groups. Fig 2 shows the proportion of participants with RD ≥ 0.5 and RD > 1.0 in the lower thigh LSV segment of either leg, by age group. A highly significant linear association between prevalence of reflux and age was noted for both RD ≥ 0.5 and RD > 1.0 ($P \leq .001$).

Table IIa shows the patterns of reflux in the femoral and long saphenous veins. In the right leg, 7.4% of participants had RD ≥ 0.5 in the CFV segment, 2.0% in both the CFV and upper LSV segments, and 1.1% in both the CFV and upper SFV segments. Only 0.5% of participants had RD ≥ 0.5 in all 3 vein segments. The results were similar for the

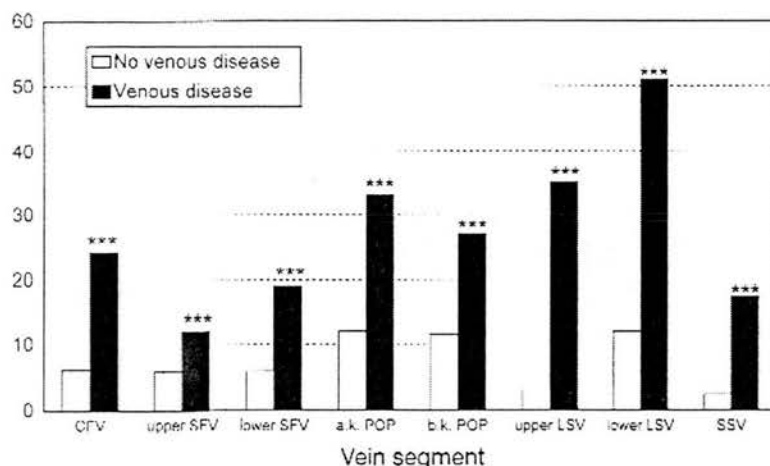


Fig 3. Age-adjusted and sex-adjusted prevalence of reflux of 0.5 seconds or more duration in either leg, at individual vein segments, in participants with and without "venous disease." CFV, common femoral vein; SFV, superficial femoral vein; a.k. POP, above knee popliteal; b.k. POP, below knee popliteal; LSV, long saphenous vein; lower LSV, lower thigh LSV; SSV, short saphenous vein.

left leg. For RD > 1.0, in each leg, 2.0% of participants had reflux in the CFV segment, and 0.3% had reflux in all 3 segments. Table IIb shows patterns of reflux in the popliteal and short saphenous vein system. In the right leg, 12.5% of participants had RD ≥ 0.5 in the above knee popliteal segment, 1.0% in both the above knee popliteal and SSV segments, and 5.7% in both the above knee and below knee popliteal vein segments. Only 1.3% had reflux in all 3 vein segments. The results were slightly lower for the left leg, whereas the prevalences were approximately halved for RD > 1.0.

When analyzed according to venous disease status (as defined in the methods section), 861 participants (516 women, 345 men) had "no disease," and 579 participants (282 women, 297 men) had "venous disease." The remaining 126 participants fell into neither category (because they had either perforators, previous varicose vein treatment, and/or grade 2/3 reticulars/hyphenwebs without trunks or CVI) and were excluded from this analysis. Of the 642 men, 46.3% had "venous disease," compared with 35.3% of the 798 women ($P \leq .001$). Those participants with "venous disease" were significantly older than those with "no disease" (mean age, 51.2 years, compared with 40.4 years) ($P \leq .001$). Fig 3 shows the age-adjusted and sex-adjusted prevalence of RD ≥ 0.5, at individual vein segments in either leg, by disease status. The prevalence of reflux was significantly higher at each vein segment in participants with "venous disease" ($P \leq$

.001). Of the 630 "disease-free" participants with complete duplex data for all 16 vein segments, 411 (65%) had no evidence of RD ≥ 0.5 in any segment. For RD > 1.0, the prevalence of reflux was also significantly higher at each vein segment in those with "venous disease" (all $P \leq .001$), although there were very few participants with "no disease" who had RD > 1.0 in the CFV or SFV segments of either leg. (CFV, n = 4, 0.5%; SFV upper, n = 3, 0.4%; SFV lower, n = 8, 1.0% [percentages are age- and sex-adjusted]). Of the 630 "disease-free" participants described above, 518 (82%) had no evidence of RD > 1.0 in any vein segment.

Table III illustrates the distribution of reflux in individual vein segments in participants with and without "venous disease." For each participant, the value was taken from the leg that showed the longer RD for each vein segment. For all segments, the median, 75th, and 95th centiles were higher in participants with "venous disease" than participants with "no disease." In participants with "no disease," the 75th centiles were all less than 0.50 seconds. The 95th centiles for the upper LSV and SSV segments were less than 0.50 seconds, and for all other vein segments they were less than 1.00 second, except the lower thigh LSV segment (6.46 seconds). When analyzed according to sex, the difference between the median RD for men and women with "no disease" was no more than 0.05 seconds for any segment. In those participants with "venous disease," the median was highest for the lower thigh LSV segment (2.30

Table III. Distribution of reflux in individual vein segments in participants with and participants without venous disease

Segment*	No venous disease (n = 861)			Venous disease (n = 579)		
	Median	IQR	95th centile	Median	IQR	95th centile
CFV	0.09	0.00-0.26	0.54	0.18	0.00-0.48	1.63
Upper SFV	0.11	0.00-0.25	0.52	0.15	0.00-0.33	1.14
Lower SFV	0.13	0.04-0.25	0.53	0.18	0.06-0.40	2.88
Above knee popliteal	0.17	0.10-0.32	0.84	0.25	0.13-0.68	2.63
Below knee popliteal	0.14	0.10-0.28	0.88	0.20	0.12-0.53	2.30
Upper LSV	0.00	0.00-0.10	0.29	0.15	0.00-4.30	8.00
Lower thigh LSV	0.11	0.05-0.16	6.46	2.30	0.10-6.97	8.00
SSV	0.10	0.00-0.14	0.27	0.13	0.10-0.24	4.08

*Value taken from the leg with the longer duration of reflux for each vein segment.

IQR, Interquartile range; CFV, common femoral vein; SFV, superficial femoral vein; LSV, long saphenous vein; SSV, short saphenous vein.

seconds). The 75th centiles for the CFV, upper and lower SFV, and SSV segments were all less than 0.50 seconds. Only the 75th centiles for the upper and lower thigh LSV segments were greater than 1.00 second (4.30 and 6.97 seconds, respectively). All the 95th centiles were greater than 1.00 second in participants with "venous disease." The sex differences in the median RD in those with "venous disease" were no more than 0.08 seconds for any segment, except the LSV segments. In participants with "venous disease," the median (inter-quartile range) RD in the upper LSV segment was 0.26 (range, 0 to 5.14) for women and 0.13 (range, 0 to 2.04) for men, and for the lower thigh LSV segment the median RD was 4.14 (range, 0.12 to 8.00) for women and 0.23 (range, 0.09 to 6.08) for men.

The relationship between duration of venous reflux in certain segments and the presence of "venous disease" in a participant was examined further. The sensitivities and specificities were calculated when different cut-off points for RD were used as a test for "venous disease." In the upper LSV segment, for a cut-off point of RD > 0.5 seconds, the sensitivity was 38.0% and the specificity 97.2%, whereas for a cut-off point of RD > 1.0 seconds, the sensitivity was 36.4% and the specificity 97.4%. In the below knee popliteal segment, for a cut-off point of RD > 0.5 seconds, the sensitivity was 26.0% and the specificity 87.9%, whereas for a cut-off point of RD > 1.0 seconds, the sensitivity was 14.2% and the specificity 95.7%.

DISCUSSION

Although duplex scanning has become the method of choice for investigation of venous reflux,¹ controversy about the method still exists. Different patient positions and techniques to elicit reflux have

been evaluated in various studies,¹³ but techniques still vary. There is also debate about what constitutes significant reflux.¹⁴ Although some authors use duration of reverse flow of greater than 0.5 seconds as a definition for significant reflux^{13,15-19} others argue that this definition would include individuals with normally functioning veins¹⁴ and use a value of greater than 1 second duration.^{20,21} Furthermore, a recent study suggested that although measuring duration of reverse flow on duplex scanning is a useful method for determining the presence of reflux, it does not correlate with the magnitude of reflux and should not be used to quantify the degree of reflux.²² We aimed to describe the prevalence and duration of venous reflux in a random population sample, to relate patterns of reflux to the overall presence of clinical venous disease, and to examine further what constitutes significant reflux.

Overall, the prevalence of reflux was very similar in the right and left legs (Table I). Generally, if the right leg segment had reflux, the likelihood that the same segment in the left leg would also have reflux was 20% to 35%, and this likelihood rose to more than 40% in the LSV segments. The choice of cut-off point for significant reflux made little difference to results in the superficial vein segments, because most reflux of at least 0.5 seconds duration was, in fact, more than 1 second in duration. This was not the case in the deep veins, however, and although 9% to 12% of participants had RD \geq 0.5 in the popliteal vein segments, only 4% to 5% showed RD > 1.

A higher prevalence of reflux in men as compared with women was found in the deep vein segments. However, this difference only reached statistical significance in 2 of the 5 deep vein segments for RD > 1.0, compared with 4 of the 5 for RD \geq 0.5. This suggests that it may be appropriate to use different

cut-off points for RD to define significant reflux in the deep veins in men and women. This might be the case if, for example, men were generally found to have larger veins that could accommodate more forward and reverse flow than women. However, in participants with "no disease," the medians for RD in the deep vein segments were only 0.02 to 0.05 seconds longer in men than in women. In addition, the higher prevalence of reflux in men does correspond with the higher prevalence of varicose veins and chronic venous insufficiency in men compared with women in this study.¹² Conversely, a higher proportion of women than men had reflux in the superficial vein segments, although these sex differences failed to reach statistical significance. The overall sex picture in the Edinburgh Vein Study was similar to that found in the Bochum Study, which examined German schoolchildren on 3 occasions during their education, at ages 10 to 12, 14 to 16, and 18 to 20 years.⁸ By the third examination, male participants had a higher prevalence of trunk varices, branch varices, and incompetent perforators than female participants, but female participants had a higher prevalence of reflux in the saphenous veins on Doppler examination. In addition, there was an increase in the prevalence of reflux, particularly in the external iliac and the saphenous veins, as the age of the children increased at successive examinations. In general, we also found a higher prevalence of reflux in the older age groups in the Edinburgh Vein Study.

When the patterns of reflux were examined, in both legs the proportion of participants with $RD \geq 0.5$ in the CFV segments greatly exceeded the proportion who also had reflux in the LSV and/or SFV segments (Table IIa). However, for $RD > 1.0$, there was less of a discrepancy. The CFV segment was the one segment in which turbulent flow was often recorded, and it may be that the size of this vein allows it to accommodate forward and reverse flow to a greater extent than any of the other segments examined, without necessarily having an incompetent distal valve. Similarly, the proportion of participants with reflux in the above knee popliteal segments exceeded the proportion who also had reflux in the below knee popliteal or SSV segments (Table IIb). Possible explanations for this include the presence of reflux down incompetent gastrocnemial veins or unusual venous drainage in the popliteal area.^{4,21} The latter possibly contributed to the relatively high number of missing results for the SSV segments in the Edinburgh Vein Study. We recognized that, by not scanning the calf veins, some questions in this study would be left unanswered.

However, on balance, we considered that duplex scanning of the calf and perforator veins would be difficult, time-consuming, and of doubtful accuracy when a noncolor Doppler system was used in a population of more than 1500 participants.

Throughout this paper, results have been presented comparing $RD \geq 0.5$ and $RD > 1.0$ as cut-off points to define significant reflux. Using $RD \geq 0.5$ as a cut-off point decreases the specificity and risks defining more normal veins as incompetent, whereas using $RD > 1.0$ as a cut-off point decreases the sensitivity and risks defining more incompetent veins as normal. There are obvious limitations in using presence of reflux in individual vein segments as a test for the presence or absence of "venous disease." Accepting these limitations, calculations of sensitivity and specificity tended to support the use of 0.5 seconds as the cut-off point for RD in the below knee popliteal vein segment as a test for venous disease. In the upper LSV, however, there was little difference in the sensitivity and specificity between $RD \geq 0.5$ and $RD > 1.0$. Further analysis of the relationships between RD in individual vein segments and specific clinical findings will be discussed in a future report. However, Table III illustrates the considerable overlap in RD in individual vein segments between those participants with and those participants without "venous disease." Although those participants with signs of venous disease had a higher prevalence of reflux in all vein segments, approximately 12% of those with "no disease" had $RD \geq 0.5$ in the popliteal and lower thigh LSV segments (Fig 3). When $RD > 1.0$ was used, these figures dropped to 3% to 4% for the popliteal vein segments, but remained at 10.7% for the lower thigh LSV segment. Whether this reflux reflects a preclinical stage in these participants before the development of varices⁸ and CVI will not be revealed until their long-term follow-up examinations.

In conclusion, we have described the prevalence of venous reflux in the general population and have shown the following results: the left and the right legs were equally affected; men had a significantly higher prevalence of reflux in the deep vein segments, whereas women had a (nonsignificantly) higher prevalence in the superficial veins; and reflux was related to the presence of "venous disease," but was also present in those without clinically apparent disease. By following-up this population, we should be able to determine the extent to which reflux can predict future occurrence of venous disease and of complications in those who already have disease.

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