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Incidence of varicose veins, chronic venous insufficiency and venous reflux in the general population and associated risk factors: The Edinburgh Vein Study Follow Up

by

Lindsay Robertson

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ABSTRACT

Chronic venous disease (CVD) is a common problem in the western world, causes considerable morbidity and has a substantial impact on the health care system in terms of cost of treatment. Most epidemiological research has focussed on the prevalence of varicose veins and ulceration. As such, evidence on the incidence and risk factors is limited. The aim of this study was to measure the incidence of C2 varicose veins, C3-C6 chronic venous insufficiency (CVI) and venous reflux ≥ 0.5 seconds duration in an adult population, and to investigate risk factors associated with the development of these conditions.

The Edinburgh Vein Study was a prospective cohort study in which 1,566 men and women aged 18-64 years randomly sampled from the general population underwent an examination comprising clinical and photographic classification of CVD, duplex scanning of the deep and superficial systems of both legs, and completed a questionnaire on lifestyle and medical history. After a 13 year period, invitations were sent to the 1456 survivors to attend a follow up examination. In total, 880 participated in the follow up study, giving a response rate of 60.4%.

The overall incidence of C2 varicose veins was 18.2% (95% CI 15.2-21.6), equivalent to an annual incidence rate of 1.4% (95% CI 1.1-1.7). There were no gender differences (p=0.78). Age was associated with the development of new C2 varicose veins the 13 year incidence rose from 9.8% in those aged 18-34 years to 25.7% in those aged 55-64 years (p<0.001). New cases of C3-C6 CVI developed in 9.2% (95% CI 7.0-11.9) of the study sample over 13 years, an annual incidence rate of 0.7% (95% CI 0.5-0.9). There were no gender differences: the 13 year incidence was 10.7% (95% CI 7.2-15.5) and 8.1% (95% CI 5.7-11.6) in men and women respectively (p=0.32). The incidence increased consistently with age, from 2.1% in those aged under 35 years to 17.1% in those aged over 55 years (p<0.001). Of all C3-C6 conditions, C3 corona phlebectatica had the highest incidence (5.3%, 95% CI 3.7-7.5). C5-C6 venous ulceration had the lowest incidence, affecting only 0.5% (95% CI 0.2-1.6) of the study sample over the 13 years.

Overall, 12.7% of participants developed new venous reflux ≥0.5 seconds duration from baseline to follow up. The 13 year incidence of superficial, deep and combined venous reflux was 8.8%, 2.6% and 1.3% respectively. Neither age nor sex were associated with the incidence of venous reflux (p>0.05). The highest incidence of reflux was in the great saphenous vein in the lower third of the thigh (4.2%, 95% CI 2.4-7.1). Venous reflux at baseline was associated with the development of new C2 varicose veins at follow up: the incidence creased linearly in those with no reflux, deep, superficial and combined reflux respectively (p<0.001).

Family history of venous disease was a significant risk factor for C2 varicose veins (age and sex-adjusted OR 1.7, 95% CI 1.1-2.7) while obesity was associated with the development of CVI (age and sex adjusted OR 4.5 (95% CI 3.3-6.9). Pregnancy appeared to be associated with the development of varicose veins but the association was not statistically significant due to small numbers. No risk factor was associated with the development of venous reflux.

The Edinburgh Vein Study is one of a few cohort studies to report the incidence of C2 varicose veins, C3-C6 CVI and venous reflux ≥0.5 seconds duration, and investigate risk factors associated with these conditions. While the results on incidence are consistent with the limited evidence from other studies, the exact effect of risk factors remains unknown. Genetic studies would help clarify whether CVD is an inherited or acquired condition. For other risk factors, results of this study could be combined with other population-based studies in a meta-analysis. The overall estimate of effect would identify the most important risk factors associated with the development of CVD and venous reflux. Finally the natural history and progression of CVD needs to be assessed. The Edinburgh Vein Follow Up Study has examined this relationship and results will help to identify those most likely to progress to more severe disease and, in turn, those who will benefit most from treatment. Appropriate, clinically proven, effective and cost-effective treatments can then be administered in an attempt to reduce the burden of CVD.

DECLARATION OF THE CANDIDATE

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person except where due acknowledgment has been made in the text.

As a research fellow on the project, I declare that I made a substantial contribution to the work of the Edinburgh Vein Study follow up. I contributed to writing grant and ethical approval applications and designed the study paperwork. I liaised with the NHS authorities and general practitioners to obtain contact details for participants. I organised the research at the Wellcome Trust Clinical Research Facility and helped to train research staff. I performed a large proportion of the data collection, including duplex ultrasound of the leg veins and classification of chronic venous disease. I instigated and performed quality control measures throughout the course of the study. I helped in the design of the study database and performed data entry and cleaning. I formulated hypotheses, conducted statistical analysis of the data, presented results orally at the American Venous Forum and was the primary author for the paper published in the Journal of Vascular Surgery [Appendix 1] and other relevant papers published throughout the course of this study. Authorisation has been granted by the Journal of Vascular Surgery and co-authors to publish the paper in this thesis.

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LIST OF ABBREVIATIONS

AVP	ambulatory venous pressure
AVVQ	Aberdeen Varicose Vein Questionnaire
BMI	body mass index
CEAP	Classification system for chronic venous disease based on clinical signs (C), aetiology (E), anatomic distribution (A) and pathophysiologic condition (P)
CFV	common femoral vein
CHI	Community Health Index
CIVIQ	Chronic Venous Insufficiency Questionnaire
CI	confidence interval
cm	centimetre
CT	computer tomography
CVD	chronic venous disease (spectrum of venous disease ranging from C1-C6 classes of CEAP)
CVI	chronic venous insufficiency (C3-C6 classes of CEAP)
CXVUQ	Charing Cross Venous Ulceration Questionnaire
DVT	deep venous thrombosis
EF	ejection fraction
EVS	Edinburgh Vein Study
FV	femoral vein
g	gram
GROS	General Register Office for Scotland
GSV	great saphenous vein
kg	kilogram
MHz	mega Hertz
mm	millimetre
MRI	magnetic resonance imaging
NHS	National Health Service
NICE	National Institute of Clinical Excellence

LIST OF ABBREVIATIONS (CONTINUED)

NHSCR	National Health Service Central Register
OF	Venous outflow
OR	odds ratio
POP	popliteal vein
PPG	photo plethysmography
PSD	Practitioner Services Division
QOL	quality of life
RVF	residual volume fraction
s	second
SF-36	36-Item Short Form Health Survey
SFJ	sapheno femoral junction
SPJ	sapheno popliteal junction
SSV	small saphenous vein
VCSS	Venous Clinical Severity Score
VDS	Venous Disability Score
VSDS	Venous Segmental Disease Score
VSS	Venous Severity Scoring System

CHAPTER 1: INTRODUCTION

1.1 CHAPTER OUTLINE

Chronic venous disease (CVD) of the legs is common in the Western world. It causes considerable morbidity in the population and treatment incurs significant costs to the health service. Knowledge on the epidemiology of CVD is essential in order to identify which patients will benefit most from treatment to slow or halt the progression of disease. This chapter will provide an overview of CVD, beginning with a definition of the term and a brief outline on the extent of the problem, in terms of prevalence and health service costs of treating the condition. (The prevalence, incidence and risk factors for CVD will be discussed in detail in Chapter 2, which reviews the literature). The anatomy of the venous system of the legs will be considered and the theories on the pathophysiological mechanisms of the disease discussed. Clinical manifestations of CVD and the various classification systems used in its diagnosis will then be presented. Methods of assessment of CVD will be outlined briefly, with a detailed section on duplex ultrasound. CVD has an impact on quality of life and tools used to measure this outcome will be presented. Treatments for CVD will then be summarised. Finally a brief synopsis of the aims, methods and results of the baseline stage of the Edinburgh Vein Study will be provided.

1.2 INTRODUCTION TO CHRONIC VENOUS DISEASE

1.2.1 Spectrum of chronic venous disease

Chronic venous disease (CVD) is a term which includes the "full spectrum of morphologic and functional abnormalities of the venous system" (Eklöf 2004). Leg symptoms associated with CVD include aching, heaviness, swelling and skin irritation (Bergan 2006). Clinical signs of CVD range in severity from uncomplicated telangiectases (spider veins) to varicose veins, skin changes and ulceration. A varicose vein, derived from the Greek word for "grape-like" (Krijnen 1997), is defined as a "subcutaneous dilated vein three millimetres in diameter or larger, measured in an upright position" (Porter 1995). Varicose veins are not just a cosmetic problem. If left untreated, they can lead to chronic venous insufficiency (CVI), including skin changes and ulceration.

1.2.2 Extent of the problem

Estimates of the prevalence of varicose veins vary widely from 2-57% in men and from 1-68% in women (Robertson 2008). This variation is discussed in Chapter 2. Venous ulceration is less common, affecting between 0.1-0.3% of the adult population (Scottish Intercollegiate Guidelines Network 2010). The natural history of venous ulceration is a continuous cycle of breakdown and healing over years, causing considerable morbidity and impaired quality of life. Pain is common, mobility and work capacity is restricted and patients often feel socially isolated (Bistreanu 2009).

1.2.3 Health service utilisation

Varicose veins pose a substantial burden on the National Health Service (NHS). According to the Information Services Division (ISD) in Scotland, 3,063 surgical procedures for varicose veins were performed in 2011/12 (www.isdscotland.org). In addition to the surgical workload, patients with varicose veins represent a large proportion of outpatient appointments in primary and secondary care (Simpson 2004). Furthermore, the management of venous leg ulcers places a significant demand on nursing services, thus incurring further costs to the NHS. The cost of treating leg ulcers is approximately £600 million per year (Scottish Intercollegiate Guidelines Network 2010). Each ulcer has been estimated to cost £2000-£4000 (Bosanquet 1992).

1.3 VENOUS SYSTEM OF THE LEG

Before the pathophysiology of CVD can be discussed, the anatomy and function of the venous system must be understood. The venous system of the legs acts as "a reservoir to store blood and as a conduit to return the blood to the heart" (Eberhardt 2005). Blood is transported from the leg to the heart through a network of veins in the lower extremity. Compared to arteries, veins have thinner walls (Meissner 2005) and "a weaker muscular layer and less elastic tissue" (Browse 1988), thus making them stiffer. There are three venous systems within the leg: the deep, superficial and perforating systems [Figure 1.1]. Leg veins are "classified according to their relationship within the muscular fascia and are located in either the deep or superficial compartment" (Meissner 2005).

1.3.1 Deep veins

Deep veins lie beneath the muscular fascia. They follow the course of major arteries as "*venae comitantes*" and, with the exception of the femoral vein, are given the same name as the arteries they accompany (Meissner 2005). Approximately 90% of venous blood leaves the legs by the deep veins (Mitchel 1994). There can often be significant variations in the deep veins, with classic anatomy observed in as little as 16% of limbs (Browse 1988). The number of veins may vary and the communication with other veins along the way can show a variety of patterns. However a general arrangement is usually apparent. In most cases, there are five major veins of the deep venous system: three below the knee and two above the knee.

Figure 1.2 displays the deep veins of the leg. The three principal conducting deep veins below the knee are usually double channels which correspond to the three main arteries in the calf; the anterior tibial, posterior tibial and the peroneal (Browse 1988). The anterior and posterior tibial veins join at the lower end of the popliteus muscle to form the popliteal vein (POP). As well as the veins from the calf and calf muscles, the POP vein is joined by the short saphenous vein (SSV) at the saphenopopliteal junction (SPJ). It runs proximally behind the knee, ascends through the popliteal fossa and passes through the adductor canal to become the femoral vein (FV) (Fronek 2004). The FV ascends through the thigh, and receives the deep femoral vein to form the common femoral vein (CFV). The CFV passes upward through the groin crease to become the external iliac vein (Fronek 2004).

1.3.2 Superficial veins

Superficial veins are large, thick-walled veins situated just under the skin within the superficial fascia (Simpson 2004). Superficial veins are a complex and variable network of collecting veins that drain blood from the skin and subcutaneous tissue and direct it to the deep system via tributary or perforating veins (Somjen 1995). The superficial veins of the leg are the great saphenous vein (GSV), which runs from groin to ankle and the small saphenous vein (SSV), which runs from ankle to knee [Figure 1.3].

The GSV is the longest vein in the body (Chen 2009). It originates in the medial foot, as part of the dorsal venous arch and runs upwards anterior to the medial malleolus before ascending the length of the tibial edge of the medial calf, passing behind the knee and forward around the medial side of the thigh (Meissner 2005). It passes through the saphenous opening in the deep fascia 3cm below to join the antero-medial side of the common femoral vein (CFV) (Browse 1988). The site where the GSV meets the CFV at the groin skin crease is termed the saphenofemoral junction (SFJ)(Caggiati 2002). The GSV lies within a clearly defined fascia compartment known as the "saphenous eye", as it has the appearance of an Egyptian eye on ultrasound examination. This distinguishable feature, particularly in the thigh region, prevents tributary veins from being mistaken for the GSV (Chen 2009). The GSV is often accompanied by tributary veins and is prone to several anatomical variations in the thigh and knee (Ricci 1999). Typically the GSV is 3-4 mm in diameter (Mozes 2001).

The small saphenous vein (SSV) originates in the lateral part of the dorsal venous arch of the foot (Meissner 2005). It ascends proximally 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 (Fronek 2004). The termination of the SSV varies. In around 60% of cases, the vein joins the popliteal vein in the popliteal fossa within 8cm of the knee joint, to form the saphenopopliteal junction (SPJ). However, in 20% of cases, it joins the GSV at varying levels in the thigh; in the remainder of cases, it has an alternative termination e.g. by joining the superficial or deep femoral vein (Browse 1988). For its entire length, the SSV lies in an inter-fascial compartment defined by muscular and superficial fascia.

1.3.3 Perforating veins

Most venous blood is transported from the superficial to the deep system via the two connecting junctions, the SFJ and the SPJ (Fronek 2004). However, blood also travels between the systems through perforating veins, which are connected to superficial veins and pass through the deep fascia to join directly with the deep veins (Meissner 2005). The number of perforating veins varies but in general there are four groups according to location: the foot, the medial and lateral calf and the thigh [Figure 1.4]. With the exception of the foot, all perforators direct blood from the superficial to the deep system (Mozes 2001).

1.3.4 Venous valves

As the blood in the legs must travel against gravity, veins contain a series of one way valves to prevent back flow of blood in an upright position [Figure 1.5] (Simpson 2004). The number of valves increases from the hip down to the calf but can vary between individuals (Eberhardt 2005). From the inguinal to the popliteal fossa there can be between two and nine deep venous valves: the CFV and the SFJ usually contain one valve each, while the FV above the adductor canal usually contains at least three, and the distal FV and POP contain between one and two valves each (Mozes 2001). The main trunk of the GSV usually has at least 6 valves while the SSV has between seven to ten closely spaced valves (Mozes 2001). Perforating veins of the calf and thigh also possess one to three valves that prevent the backflow of blood from the system to the superficial system (Meissner 2005).

Valves are formed from folds of endothelium and are supported by thin sheets of collagen and smooth muscle (Meissner 2005). They have two cusps which remain open during rest in the supine position and close through the force of the retrograde blood flow (van Bemmelen 1990). Valves work in tandem with venous muscle pumps, which eject a sufficient force of blood up towards the heart, ensuring valve closure (Padberg 2001).

1.3.5 Calf muscle pump

Venous muscle pumps are located in the foot, calf and thigh. Of the three, the calf muscle pump has the "largest capacitance, generates the highest pressures, and is of greatest importance" (Meissner 2005) and as such, is often termed the "peripheral heart" (Fronek 2004). Figure 1.6 displays the mechanism of the calf muscle pump. During contraction, the gastrocnemius and soleus muscles drive blood into the deep veins, where the valves prevent backflow (Meissner 2007b). During relaxation, blood is drawn from the superficial to the deep system through perforating veins (Eberhardt 2005). When exercise ceases, the veins slowly fill until normal resting venous pressure is achieved (Meissner 2007b).

1.3.6 Venous reflux

Reverse flow of blood is prevented by one-way valves in the veins which snap shut, holding the column of blood until the next calf muscle contraction occurs. However, the valve will only shut when the gradient of the retrograde blood flow is of sufficient velocity to force the cusps to close completely (van Bemmelen 1990). The normal time taken for the velocity to reach the required force in an upright position is less than 0.5 seconds, during which some reverse blood flow will occur (van Bemmelen 1990). However if the reverse blood flow persists for longer than 0.5 seconds in an upright position, this is termed pathological "reflux" (Meissner 2005). Venous reflux develops when "venous pressure is increased and return of blood is impaired through several mechanisms" (Burnand 2001).

1.4 PATHOPHYSIOLOGY OF CHRONIC VENOUS DISEASE

According to an International Consensus Committee on Chronic Venous Disease, CVD is "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 1995). The term CVD covers the whole spectrum of clinical severity, from telangiectases and reticular veins to varicose veins, skin changes and ulcers (Meissner 2007a). An ad hoc committee of the American Venous Forum determined that as spider and reticular veins are highly prevalent in the adult population, the term "disease" is not appropriate for these conditions (Eklöf 2004). Therefore, when discussing pathophysiology, the term CVD will only cover varicose veins and CVI.

Primary CVD is defined as "venous dysfunction of unknown cause but not of congenital origin", whereas secondary refers to "an acquired condition which has led to CVD, for example, deep vein thrombosis" (Porter 1995). A varicose vein is defined as a "subcutaneous dilated vein three millimetres in diameter or larger, measured in an upright position" (Porter 1995). The term CVI does not include varicose veins but "refers more specifically to the spectrum of skin changes associated with sustained venous hypertension" (Meissner 2007a). Venous hypertension is defined as a "failure to reduce venous pressure with exercise' (Meissner 2007b), and is caused by reflux. Although the exact aetiology of reflux is unknown, several theories have been proposed and will now be discussed.

1.4.1 Valvular incompetence

The valvular incompetence theory proposes that valve failure is the initial pathological change that causes varicose veins. Valve failure may be primary as a result of weakness in the valve, or secondary to DVT or phlebitis (Burnand 2001). Incompetence of the valves in the junctions connecting the two venous systems (SFJ and SPJ) or the perforating veins, allows pathological reflux > 0.5 seconds duration to occur. In turn, reflux causes blood stasis and increased hydrostatic pressure in the leg (Eberhardt 2005). Venous hypertension causes the vein wall to weaken, the vein dilates and becomes varicose (Lim 2009). Furthermore, as the vein dilates, the valve cusps separate further, thus worsening the valvular incompetence (Lim 2009). This constant state of venous hypertension can lead to hyperpigmentation, subcutaneous tissue fibrosis (lipodermatosclerosis), and eventual ulceration (Eberhardt 2005). The theory also proposes that valvular incompetence progresses in a descending fashion, starting in the SFJ or SPJ and progressing down the leg (Raffetto 2008, Somers 2006).

Despite the fact that reflux is often the main haemodynamic abnormality in primary CVD, there is little evidence to support the valvular incompetency theory. In fact, evidence has shown that vein dilation often occurs before valvular incompetence (Meissner 2007a). Furthermore, the theory of sequential valve failure has also been contradicted by evidence that varicose veins are often found below competent valves in the SFJ (Labropoulos 2000, Somjen 1995). Instead, ultrasound findings suggest that primary valvular incompetence is "a multicentric process the develops simultaneously in discontinuous venous segments" (Labropoulos 1997).

1.4.2 Vein wall abnormality

The vein wall theory hypothesises that the primary cause of CVD is a structural or biochemical abnormality of the vein wall (Meissner 2005). Changes in the collagen, elastin and smooth muscle layers of saphenous varicose veins have been proposed (Clarke 1992, Vanhoutte 1997) and significantly reduced vein wall elasticity has been detected in affected patients (Raffetto 2008, Somers 2006). This evidence suggests that structural changes in the vein wall precede both symptomatic varicose veins and valvular incompetence. It is presumed that reflux occurs when the weakened vein wall dilates, causing the valve cusps to stretch and subsequent failure of the valve to close completely (Meissner 2005). Consequently the high venous pressure in the leg leads to varicose veins and can eventually result in oedema, inflammation, skin changes and ulceration (Eberhardt 2005).

While it is unknown whether the structural changes in the vein wall are primary or a consequence of a pathological process, various factors associated with haemodynamic abnormality have been suggested, including hypoxia, changes in enzyme activity, mechanical stretch, low shear stress and underlying defects in venous tone (Haardt 1987, Lowell 1992, Michiels 1997, Michiels 2002)

1.4.3 Venous obstruction

Venous obstruction of the deep system is a common cause of secondary CVD (Johnson 1995). A thrombus in a deep vein may damage the valve directly or indirectly by causing venous stenosis, which leads to vein-wall injury and dilatation (Eberhardt 2005, Ibrahim 1996). Normal venous outflow of blood is restricted and the venous pressure within the calf increases, leading to reflux. As a result of this process, the calf muscle pump can become dysfunctional (Eberhardt 2005). Lipodermatosclerosis and ulceration are seen more frequently in patients with varicosities secondary to venous obstruction (Lees 1993), suggesting that venous obstruction is a significant mechanism in the pathogenesis of CVI (Neglén 2003). Obstruction of the popliteal vein in particular, has been shown as an important determinant of the severity of CVI (Meissner 1998).

1.4.4 Dysfunction of the calf muscle pump

While calf muscle pump dysfunction is rarely a primary cause of reflux, it is often a secondary outcome of severe venous reflux or obstruction (Eberhardt 2005). An ineffective calf muscle pump results in blood not being emptied out of the leg, causing venous hypertension (Eberhardt 2005). Evidence has shown that calf muscle pump dysfunction is a major mechanism for the development of superficial vein incompetence and venous ulcers (Araki 1994, Christopoulos 1989). The relationship between calf muscle pump and ulceration can be partially explained by the reduced range of ankle movement associated with this condition (Back 1995).

Despite the theories regarding the aetiology of venous reflux, the precise pathophysiology of CVD remains unknown. It is important to consider that the venous system of the legs is comprised of three components: valves, vein walls and haemodynamics of venous blood flow (Lim 2009). For a venous system to function normally, the three components must all function effectively (Ibrahim 1996). As the three components are interdependent, when one is disrupted in any way, the functioning of the others is affected. Any changes can further affect the initial dysfunction, triggering a repetitive cycle (Lim 2009). By the time varicose veins are symptomatic, "all components are already disrupted, making it difficult to pinpoint the primary stimulus and map the sequence of pathological events" which led to the varicosity (Lim 2009).

1.4.5 Predisposing factors

Other, non-pathological factors may predispose to the development of CVD. Varicose veins are generally accepted as being more common in women than in men and to increase in prevalence with age. There is some evidence that family history of CVD, pregnancy and DVT are risk factors. Other postulated risk factors include, obesity, prolonged standing, constipation, heavy lifting, lack of exercise and cigarette smoking. However, evidence on these risk factors is variable and inconclusive. Risk factors for CVD will be discussed in more detail in Chapter 2, which reviews the literature.

1.5 CLASSIFICATION OF CHRONIC VENOUS DISEASE

1.5.1 Clinical manifestation of chronic venous disease

The manifestations of CVD range in severity from uncomplicated telangiectases and reticular veins, to varicose veins and advanced skin changes. Telangiectases [Figure 1.7], are small intradermal veins less than 1mm, while reticular veins [Figure 1.8] are blue sub-dermal veins 1-3mm in diameter (Eklöf 2004). There have been various definitions of varicose veins but they are generally described as dilated, subcutaneous veins 3mm in diameter or larger, that become progressively more tortuous and distended [Figure 1.9] (Eklöf 2004). Apart from the obvious cosmetic issue regarding the appearance of the legs, patients with varicose veins also report a dull ache or heaviness in the legs, particularly after periods of prolonged standing (Ibrahim 1996).

Symptoms of CVI range by severity of the condition. Mild CVI comprises submalleolar venous 'flare' at the ankle known as corona phlebectatica [Figure 1.10] and oedema (Eklöf 2004). Oedema [Figure 1.11] is a swelling caused by the accumulation of fluid, which begins in the gaiter region and ascends up the leg (Eberhardt 2005). Moderate CVI comprises cutaneous changes, including a brown discolouration in the gaiter region called pigmentation [Figure 1.12], eczema-like dermatitis [Figure 1.13], inflammation and fibrosis of subcutaneous tissue, called lipodermatosclerosis [Figure 1.14] and atrophic white skin, known as atrophie blanche [Figure 1.15] (Eklöf 2004). Severe CVI comprises healed and active ulceration [Figures 1.16 and 1.17 respectively], defined as "a full-thickness defect of the skin that fails to heal spontaneously and is sustained by CVD" (Eklöf 2004).

1.5.2 Basle classification

The Basle, or Widmer classification, was the first attempt to standardise the classification of chronic venous disease (Widmer 1978). Telangiectasia, reticular, and varicose veins were classified separately with grades 1, 2 and 3 applied to each to represent the severity of the condition; mild, moderate and severe. CVI was also split into three categories according to severity of disease [Appendix 2]. The Basle classification used only clinical criteria, which was subjective as it involved assessment by examination of the legs without objective measurements using instruments.

1.5.3 CEAP classification

In 1994, an ad hoc committee of the American Venous Forum developed a classification system, in an attempt to standardise the evaluation of severity of CVD (Porter 1995). Since then, subsequent revisions and improvements have been made based on new knowledge (Eklöf 2004). The CEAP classification system includes not only the clinical symptoms (C) of CVD, but also considers the etiology (E), anatomic distribution (A), and the pathogenic mechanism (P), and produces a score based on the severity of disease [Appendix 3]. Clinical signs in the affected leg are categorised into seven classes designated C0 to C6, which are further categorised by the presence or absence of symptoms. The etiologic classification is based on congenital, primary or secondary causes of venous dysfunction. The anatomical classification identifies the deep, superficial or perforating venous systems affected, where multiple venous segments may be involved. Finally, the pathophysiological classification determines the underlying mechanism causing CVD including reflux, venous obstruction, or both.

CEAP is a "valuable tool in the objective valuation, providing a system to standardise venous disease classification, with emphasis on the manifestations, cause and distribution of venous disease" (Eberhardt 2005). It is now widely accepted and is used in many large observational studies (Chiesa 2005, Criqui 2003, Rabe 2010, Schultz-Ehrenburg 1992). Nevertheless, it has limitations. It is a subjective measure and does not allow an assessment of change in response to treatment. Other than clinical class, CEAP does not estimate the severity of venous disease: varicose veins can be present with or without oedema, skin changes and ulceration (Meissner 2007b). To complement the CEAP system and measure the severity of CVD, a committee on Venous Outcome Assessment of the American Venous Forum developed a venous severity scoring system (Rutherford 2000).

1.5.4 Venous Severity Scoring System

The Venous Severity Scoring (VSS) system provides a numeric score based on 3 components: Venous Clinical Severity Score (VCSS), Venous Segmental Disease Score (VSDS) and Venous Disability Score (VDS) [Appendix 4] (Rutherford 2000). The VCSS consists of ten clinical characteristics of CVD (pain, varicose veins, venous oedema, skin pigmentation, inflammation, induration, number of ulcers, duration of ulcers, size of ulcers, and compressive therapy) with four grades (absent, mild, moderate, severe). The VSDS provides the number of venous segments with reflux or obstruction and the VDS is based on the ability to perform normal daily activities with or without the use of compression stockings (Rutherford 2000).

The venous severity scoring has been shown to be useful in evaluating the response to treatment, particularly superficial venous surgery (Kakkos 2003, Vasquez 2007). However, results the on the internal and external validity are contradictory. One study reported high inter-observer and intra-observer agreement (Vasquez 2007) but another study measured inter- and intra-observer variability in grading CVD (Meissner 2002). Furthermore, a survey of angiologists determined that the VCSS was not as effective as CEAP in diagnosing conditions at the lower end of the CVD spectrum (CEAP classes C1 to C3) (Perrin 2006).

1.6 QUALITY OF LIFE WITH CHRONIC VENOUS DISEASE

For chronic conditions such as CVD, patient-based assessments of quality of life (QOL) provide important information not only on the burden of disease, but also on the change in illness over time (Kahn 2004). Furthermore, as CEAP may not accurately reflect the patients' own perceptions of CVD severity, they provide a "needed adjunct to physician-based assessments" (Meissner 2007b). Patient based QOL instruments include both generic and disease-specific surveys. Generic surveys assess overall state of wellbeing, whereas disease-specific surveys focus on particular aspects of the disease process and are sensitive to specific outcomes (Vasquez 2010). A combination of generic and disease-specific tools surveys has been advocated for measuring QOL with CVD (Kundu 2007).

1.6.1 Generic quality of life instruments

Generic QOL instruments include the Medical Outcomes Study Short Form (SF-36), EuroQol, the Nottingham Health Profile and the Sickness Impact Profile. The SF-36 is the most commonly used, and determines both physical and mental health (Davies 2006). These two health states are categorised into eight domains, including physical and social functioning, limitations due to physical or emotional problems, mental health, pain, vitality and health perceptions. The SF-36 produces a score ranging from 0 to 100, with higher scores indicating better general health perception (Vasquez 2010). For measuring the CVD, it is preferable to be combine the SF-36 with a disease-specific QOL instrument (Meissner 2007b)

1.6.2 Disease-specific quality of life instruments

There are several disease-specific QOL instruments. The Aberdeen Varicose Vein Questionnaire (AVVQ) (Garratt 1996), The Charing Cross Venous Ulceration Questionnaire (CXVUQ) (Smith 1999), and The Chronic Venous Insufficiency Questionnaire (CIVIQ) (Launois 1996), only look at specific conditions and therefore cannot be applied to the full spectrum of CVD. However, an instrument, set up by the Venous Insufficiency Epidemiological and Economic Study (VEINES), evaluates all aspects of venous disease, including CEAP classes, post-thrombotic syndrome, and venous thromboembolism (Lamping 2003).

The VEINES instrument is focussed on physical symptoms rather than psychological or social aspects of CVD. It consists of 35 items split into two sections. The first is a QOL questionnaire (VEINES-QOL), comprising 25 items quantifying disease effect on quality of life. The second section is a symptom questionnaire (VEINES-Sym), with 10 items measuring physical symptoms. Patient responses are made on a 2- to 7-point scale rating intensity, frequency, and agreement. A summary score is generate for each section, with higher scores representing a better quality of life (Lamping 2003). The VEINES-QOL/Sym was tested and deemed to be an acceptable, reliable and valid tool (Abenhaim 1997).

1.7 INVESTIGATION OF CHRONIC VENOUS DISEASE

Initial assessment of a patient with CVD begins with a clinical history and physical examination of the legs, with the patient in an upright position to allow maximal distention of the veins (Eberhardt 2005). Inspection of the legs allows the physician to identify the visual signs and symptoms, assess their severity and determine whether they are associated with CVD or another co-existing non-venous pathology. As the initial examination does not always indicate the nature and extent of the underlying pathology, objective testing is required to confirm the diagnosis, determine the aetiology of disease and identify the particular vein segment affected. This section will briefly review the diagnostic tests available in the assessment of venous reflux. Tests are divided into two categories: non-invasive testing (venous duplex imaging, continuous wave Doppler ultrasound, photoplethysmography and air plethysmography) and invasive testing (phlebography and ambulatory venous pressure).

1.7.1 Duplex ultrasound

Physics and principles

Ultrasound refers to any sound wave of frequency higher than 20 KHz, which cannot be heard by the human ear (Oxford English Dictionary 2012). In an ultrasound machine, a transducer containing piezoelectric crystals transmits high frequency sound waves through an electrical current. When the sound waves enter the body, they are absorbed, attenuated or reflected back by the tissues. As body tissues are various densities, they reflect the sound waves at different degrees. Sound waves reflected back to the transducer are converted into electrical signals. The electrical signals form a detailed image of differing shades of brightness (B-mode ultrasound) based on the amplitude of the reflected sound wave and the time taken to reflect back to the transducer (Sofferman 2011).

Ultrasound uses the principle of the "Doppler effect" to measure blood flow in a vessel. The theory is that the "frequency of a sound wave reflected from a moving object changes in proportion to the velocity of the reflecting object" (Donnelly 2000). The change in the frequency of the reflected sound measures the velocity of movement of the object (Sofferman 2011). To measure blood flow, the transducer is coupled with acoustic gel to prevent sound being reflected at the air-skin surface. The transducer is directed towards a vein and sound waves are reflected from the red blood cells. Movement of the red cells causes a change in frequency (Doppler shift) in the reflected sound waves, which is proportional to the blood flow velocity (Hass 2013).

Duplex ultrasound to detect venous reflux

Venous duplex ultrasound "combines B-mode imaging of the deep and superficial veins with pulsed Doppler assessment" to provide anatomical and functional information on blood flow (Eberhardt 2005). Specific veins in the deep, superficial and perforating systems can be identified and the presence, direction and velocity of blood flow at different locations within the vein can then be established. The addition of colour frequency mapping allows the moving blood to be represented as a colour [Figure 1.18]. 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. Colour systems have the advantage not only of rapid identification of the veins, thus reducing scanning time , but they also enable visualisation of blood flow and venous reflux in the veins directly (Donnelly 2000).

High frequency linear array transducers ranging from 7-13.5 MHz are used to detect venous reflux (Coleridge-Smith 2006). The examination is best done with the patient in a vertical position to allow gravity to demonstrate reflux (Allan 1999). The deep veins of the thigh and the calf, the GSV and SSV, perforators and other communicating veins are assessed for reflux. Reflux can be initiated by three methods: the Valsalva manoeuver, manual calf compression or pneumatic cuff compression of the calf with subsequent sudden release or rapid deflation (Nicolaides 2000). Cuff measurements have been shown to be the most accurate in diagnosing reflux as they provide a standardised stimulus (Broholm 2011, Markel 1994).

Reflux is diagnosed where there is "clear reversed flow of blood occurring after the period of forward flow in the vein segment being scanned" (Allan 1999). A short period of reverse blood flow as the cusps of the valve close is normal. However, a reflux time of greater than 0.5 seconds is classified as pathological reflux. Although 0.5 seconds is the accepted measure of reflux, the cut-off point has been debated and a more refined definition with a variable cut-off based on location has been suggested. In particular it is recommended that the reflux cut-off value for the femoropopliteal veins should be greater than 1 second (Labropoulos 2003).

According to a consensus committee on CVD, duplex ultrasound is considered to be the 'best-documented non-invasive method of quantifying reflux by measuring reflux duration' (Porter 1995). Evidence has shown that duplex ultrasound reflects the degree and distribution of reflux more accurately than descending venography (Neglen 1992). Furthermore, a study of 118 limbs determined that duplex ultrasound was accurate in measuring the degree and distribution of reflux correlated to the severity of CVD, with high sensitivity (83%) and specificity (86%) (Neglén 1993). Duplex ultrasound has also been shown to produce repeatable results with 94% agreement between reflux measures when a cut-off point of ≥ 0.5 seconds was used and the patient was in a standing position (Lurie 2012). Measurements of reflux made using an inflatable cuff have been shown to be more accurate than manual compression of the limb in diagnosing reflux, particularly in the deep venous system (Broholm 2011)

Duplex ultrasound in epidemiological studies

Duplex scanning has been used several epidemiological studies of CVD (Allan 2000, Cesarone 2002, Criqui 2003). It is non-invasive and painless. However, the scan is time consuming. Furthermore the observer must be trained in ultrasound scanning and understand the anatomy of the leg veins. As epidemiological studies of reflux require several observers taking measurements over a long study period, they are prone to observer variability. Studies often provide detailed scanning protocols and extensive training to reduce such variability. It is imperative that observers are monitored regularly to check observer variability and ensure accuracy of reflux data.

1.7.2 Continuous wave Doppler ultrasound

Continuous wave Doppler ultrasound is a useful test for detecting reflux at the SFJ and SPJ. A limitation is that it cannot insonate an individual vein as it detects flow in any artery or vein in the path of the ultrasound beam. At the groin, reflux can be in the GSV, its tributaries or the CFV. Doppler ultrasound cannot identify the exact site of reflux nor can it detect the SPJ. For these reasons, duplex ultrasound is favoured.

1.7.3 Photoplethysmography

Photoplethysmography (PPG) is a non-invasive test where a light sensor detects changes in the blood flow as the veins fill and empty after calf muscle contractions. PPG has several limitations. It cannot determine the specific anatomic distribution of reflux. Secondly, refilling time is dependent on the size of the vein to be filled. Deep veins are larger in diameter, carry a large volume of blood and therefore naturally refill quickly (Eberhardt 2005). A short refilling time would incorrectly suggest venous reflux. With such limitations, suspected reflux should always be confirmed by duplex ultrasound.

1.7.4 Air-plethysmography

Air plethysmography can measure venous reflux, obstruction and calf muscle pump dysfunction (Christopoulos 1988). Changes in limb volume are measured by air displacement in a cuff while the patient performs a series of tiptoe movements to empty and fill the venous system (Eberhardt 2005). A thigh cuff is rapidly inflated and deflated so that the adequacy of venous outflow can be measured. Rate of refill is used to determine the presence and severity of venous reflux, while the ejection fraction corresponds to the calf muscle pump function.

1.7.5 Phlebography

Phlebography was the "gold standard" but has been replaced by non-invasive imaging. Dye is injected into the foot or at the groin, allowing visualisation of the vein and blood flow. Phlebography measures the extent of reflux in the superficial or deep veins, provides information on valves, and differentiates primary from secondary disease (Meissner 2007a). However, it is an invasive procedure associated with complications including allergic reaction, infection, vein damage and exposure to radiation.

1.7.6 Ambulatory venous pressure

Ambulatory venous pressure (AVP) is the gold standard in detecting venous hypertension in the leg (Masuda 2001, Nicolaides 1986). It is an invasive technique in which a needle is inserted into the vein in the foot to measure the change in pressure between rest and exercise. AVP can also distinguish deep from superficial reflux (Eberhardt 2005). As it provides information on haemodynamics only, it supplements the anatomical information provided by duplex ultrasound or phlebography.

1.8 TREATMENT OF CHRONIC VENOUS DISEASE

Treatment of CVD is based on severity of disease and reflux imaging results. At first, all patients are treated conservatively and advised to elevate their legs to prevent oedema. If conservative measures fail or provide an unsatisfactory response, then further treatments, including interventional or surgical procedures, are considered based on anatomical and pathophysiological features of the disease. Patients with CEAP classes 4 to 6 are often referred to a vascular specialist and undergo invasive treatment in an attempt to slow or stop progression of disease.

1.8.1 Conservative treatment

Conservative measures aim to "reduce symptoms and help prevent the development of secondary complications and the progression of disease" (Eberhardt 2005). The preferred form of treatment is compression therapy. Compression stockings oppose the hydrostatic forces of venous hypertension, thus reducing venous reflux and improving venous pumping (Kurz 1999, Partsch 1999). Worn compliantly, they have been shown to reduce pain, oedema and skin changes (Motykie 1999), improve calf muscle pump function and reduce reflux in vein segments (Ibegbuna 2003, Zaijkowski 2002), and heal and prevent the recurrence of ulcers (Mayberry 1991). Other conservative treatments include venoactive drugs for the relief of symptoms of CVD (Kurz 1999) and exercise programs to improve calf muscle pump function (Padberg 2004).

1.8.2 Interventional treatment

Sclerotherapy is the injection of an irritant into an empty vein, resulting in complete venous destruction (Worthington-Kirsch 2005). According to a consensus statement, it is the preferred treatment for obliterating telangiectases and reticular veins without reflux (Baccaglini 1997). Although sclerotherapy can treat varicose veins, it cannot cure the underlying pathology and therefore cannot prevent new varices forming (Baccaglini 1997). As a result, it is often used in conjunction with surgical procedures in the correction of CVD (Eberhardt 2005). Complications of sclerotherapy include hyperpigmentation of the surrounding skin over the thrombosed vein and thrombophlebitis (Simpson 2004).

Recent advances in interventional treatment include endovascular radiofrequency or laser therapy ablation, in which controlled thermal energy, damages the vein wall leading to thrombosis, fibrosis and vein obliteration (Eberhardt 2005). This technique can be used an alternative to surgery when there is reflux in the GSV. Both techniques have reported high obliteration rates and improvement of symptoms (Merchant 2002, Min 2003). Furthermore, two randomised controlled trials determined that they are associated with fewer complications and a faster recovery time than surgery (Darwood 2008, Rasmussen 2011).

1.8.3 Surgical treatment

Surgical treatment of superficial reflux involves removing the saphenous vein (Bergan 2004). Methods of removing the GSV include "ligation alone, ligation with groin to knee stripping and ligation with ankle to groin stripping" (Meissner 2007a). Ligation without stripping has been deemed inadequate as the competent vein left in the thigh continues to reflux (Cheatle 2005). Ligation and stripping of the GSV has been shown to improve venous haemodynamics, eliminate concomitant deep venous reflux, provide symptomatic relief and assist in ulcer healing (MacKenzie 2004, Padberg 1996). However, approximately one-third of patients develop recurrent varicose veins after surgery (Fischer 2001). Neovascularisation in the groin causes recurrence after saphenous stripping and is commonly seen following this procedure (Fischer 2002).

1.8.4 Management of venous leg ulcers

There is wide variation in the management of venous leg ulcers including hospital and primary care clinics and home visits. Aggressive wound care is required to minimise infection. A variety of hydrocolloids and foam dressings control wound fluid drainage and resultant maceration of the skin. In the presence of an infected ulcer, silver-impregnated dressings have been effective in controlling infection and restoring tissue integrity. Surgical repair of deep venous valves is an effective procedure in patients with a non-healing ulcer (Meissner 2007a), with high rates of healing success at 5 years and beyond (Masuda 1994).

1.9 THE EDINBURGH VEIN STUDY

The Edinburgh Vein Study was the first large scale study in the United Kingdom to measure CVD in the general population. It was a cross-sectional survey which measured the prevalence of varicose veins and CVI. Additionally, it aimed to establish a cohort of men and women in the general population as a basis for future studies to examine the natural history, estimate the incidence and identify risk factors associated with the development of CVD.

Between 1994-1996 men and women aged 18-64 years were randomly sampled from the registers of twelve general practices in Edinburgh. In total, 1,566 people took part and underwent a clinical examination of their legs. The examination included a self-administered questionnaire, height and weight, leg examination and classification of CVD using the Basle system, plus photographs, duplex scanning of the deep and superficial systems of both legs.

The age-adjusted prevalence of trunk varices (grades 1-3) was 39.7% in men and 32.2% in women. The majority of affected subjects had mild (grade 1) trunks. Telangiectases and reticular varices were very common, each affecting over 80% of subjects. The age-adjusted prevalence of CVI was 9.4% in men and 6.6% in women. Risk factors measured included pregnancy, family history of venous disease, smoking, mobility at work, obesity and fibre intake. No consistent association was shown with any risk factor. Results suggested that obesity might to be a risk factor for varicose veins in women only while self-reported family history suggested a familial susceptibility.

1.10 CHAPTER SUMMARY

This chapter has outlined the symptoms and pathophysiology of CVD, its diagnosis and treatment. The Edinburgh Vein Study was one of the first large-scale studies of venous disease in a UK population. Results on the prevalence of CVD and associated risk factors have been presented previously (Evans 1999, Lee 2001). The study was designed with the aim that participants at baseline would form a cohort who could be followed up, in order to measure the incidence of CVD and identify factors that predispose individuals to this condition. This PhD thesis is based on the design and results of the follow up stage of the Edinburgh Vein Study.

FIGURE 1.1 VENOUS SYSTEMS OF THE LOWER LIMB

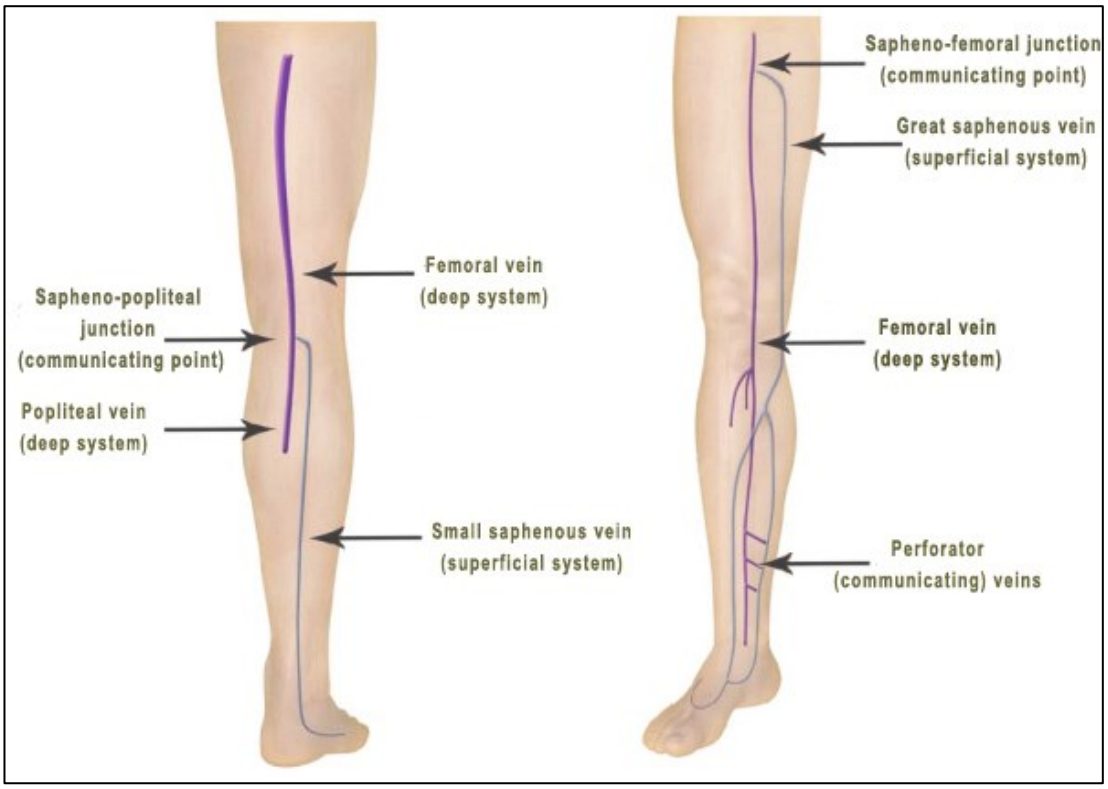

Figure reprinted with permission from Medivisuals.

FIGURE 1.2 DEEP VEINS OF THE LEG

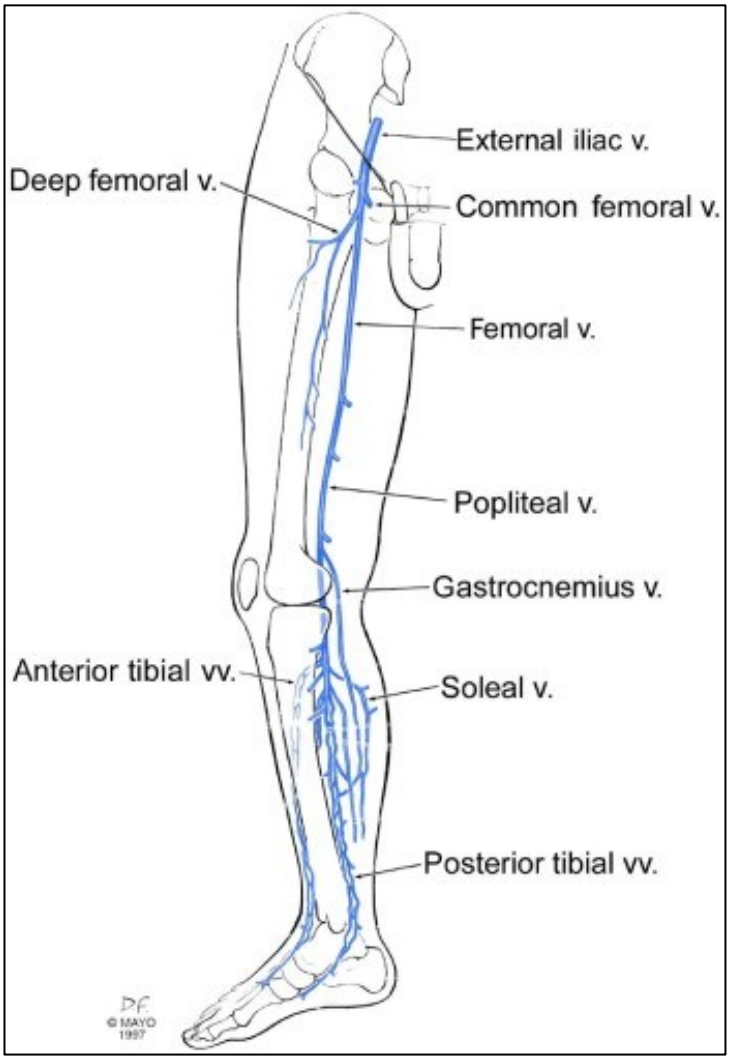

Figure extracted from Meissner 2007b and reprinted with permission from Elsevier.

FIGURE 1.3 SUPERFICIAL VEINS

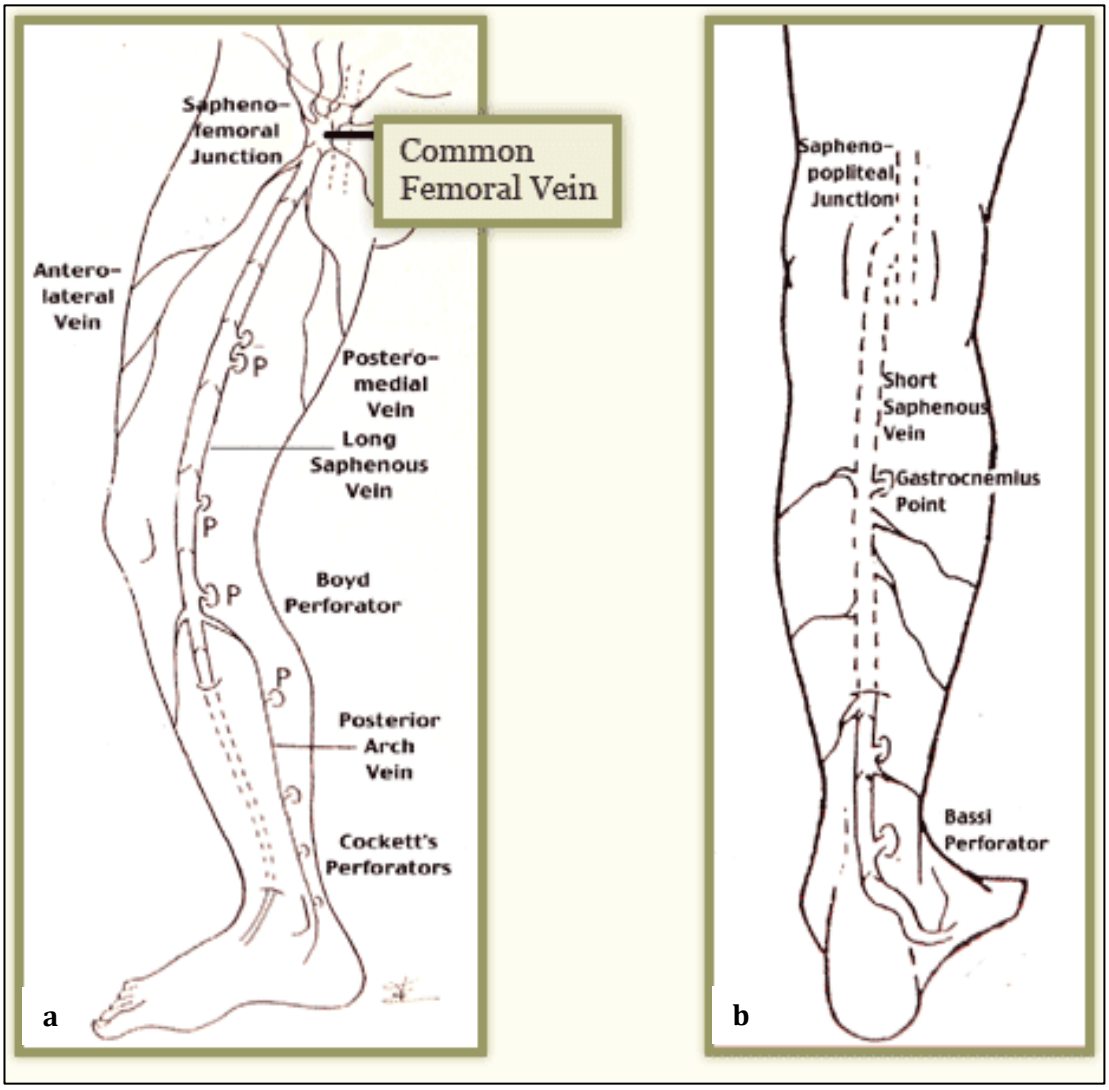

Figure reprinted with permission from Total Vein Care.

Footnote:

(a) Long saphenous vein now termed great saphenous vein

(b) Short saphenous vein now termed small saphenous vein

FIGURE 1.4 PERFORATING VEINS OF THE LEG

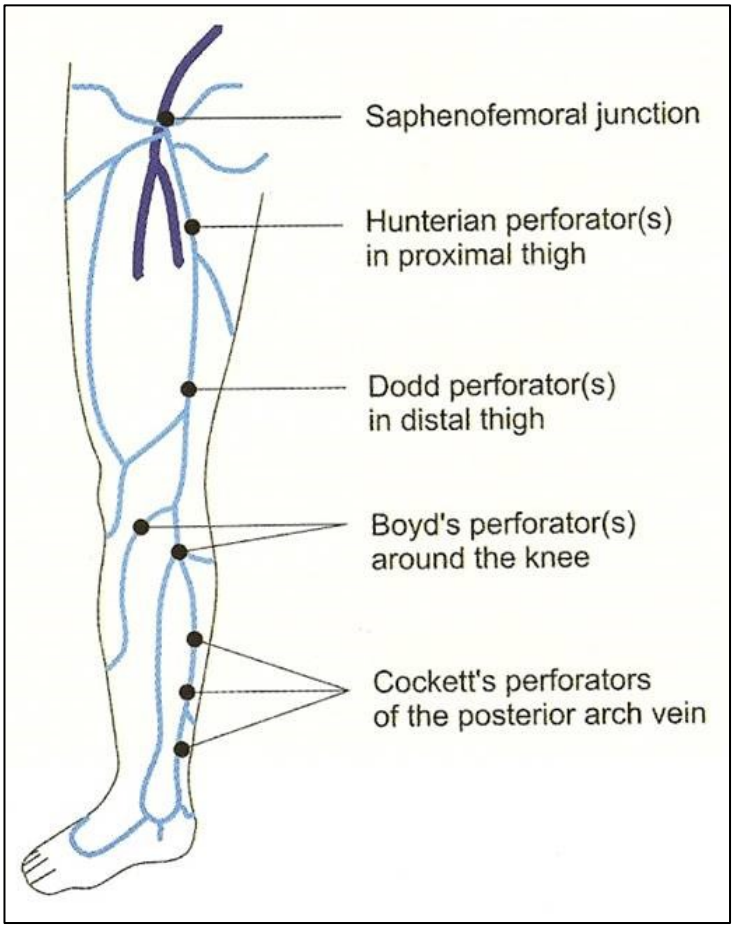

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FIGURE 1.5 VENOUS VALVES

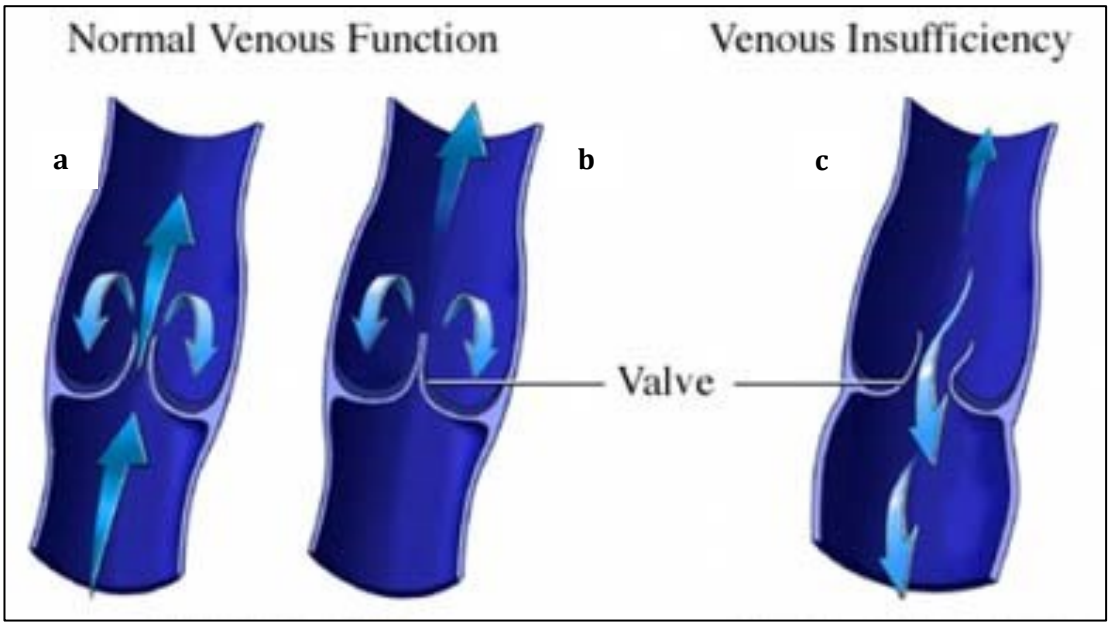


Figure reprinted with permission from Nucleus Medical Media. Inc.

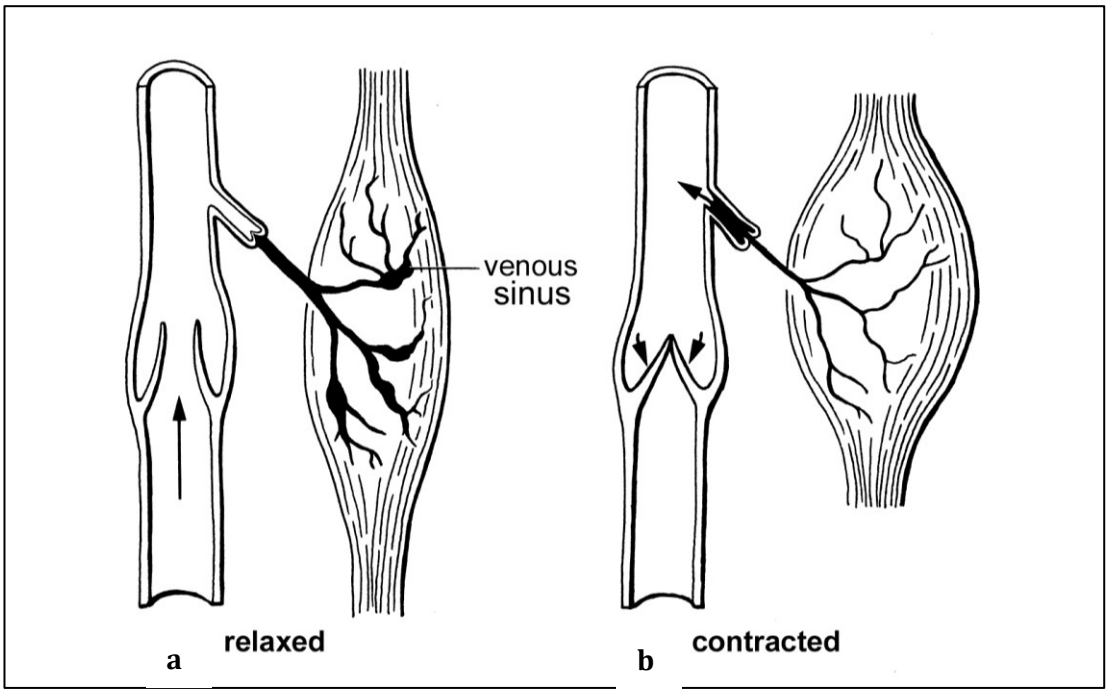
Footnote:

(a) Upward blood flow through an open valve

(b) Competent valve with the cusps fully closed preventing reverse blood flow (reflux)

(c) Incompetent valve where the cusps fail to close completely resulting in reverse blood flow (reflux)

FIGURE 1.6 ACTION OF THE CALF MUSCLE PUMP



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Footnote:

(a) Calf muscle is relaxed, the valve is open and blood accumulates in the vein

(b) Calf muscle contracts squeezing blood into the vein, the valves are closed preventing reverse flow and blood is directed towards the heart.

FIGURE 1.7 C1 TELANGIECTASES

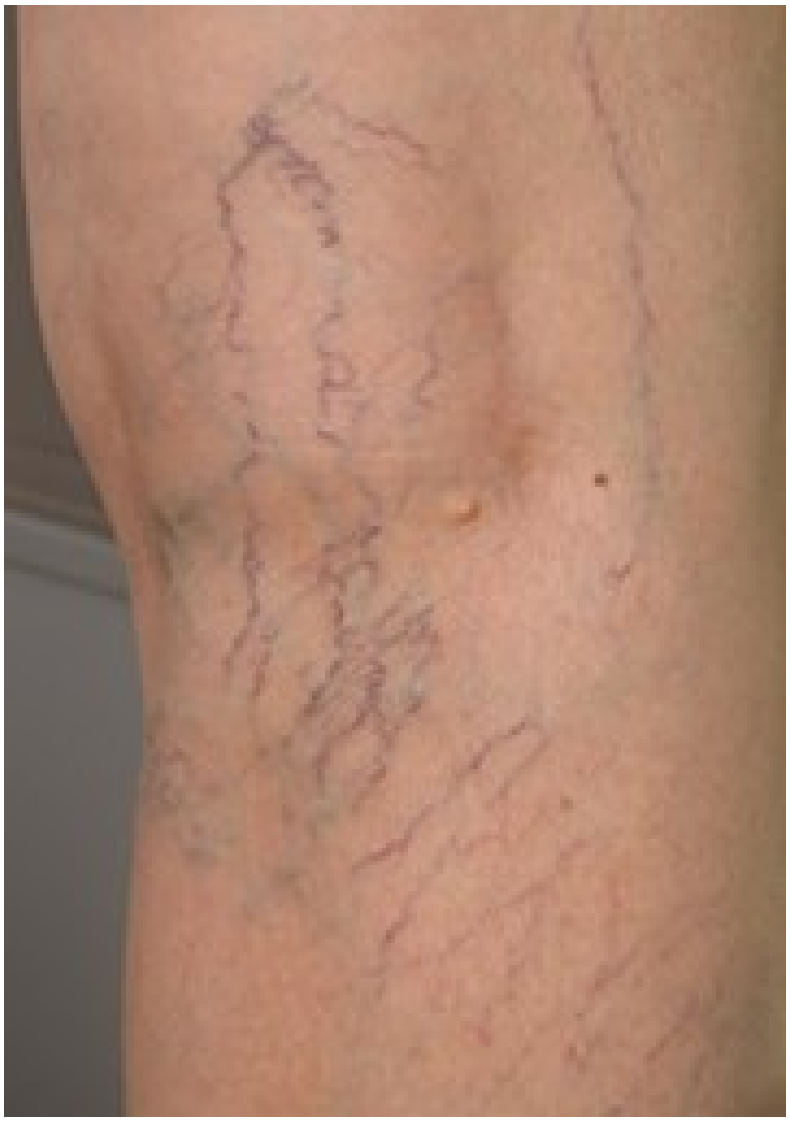

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FIGURE 1.8 C1 RETICULAR VEINS

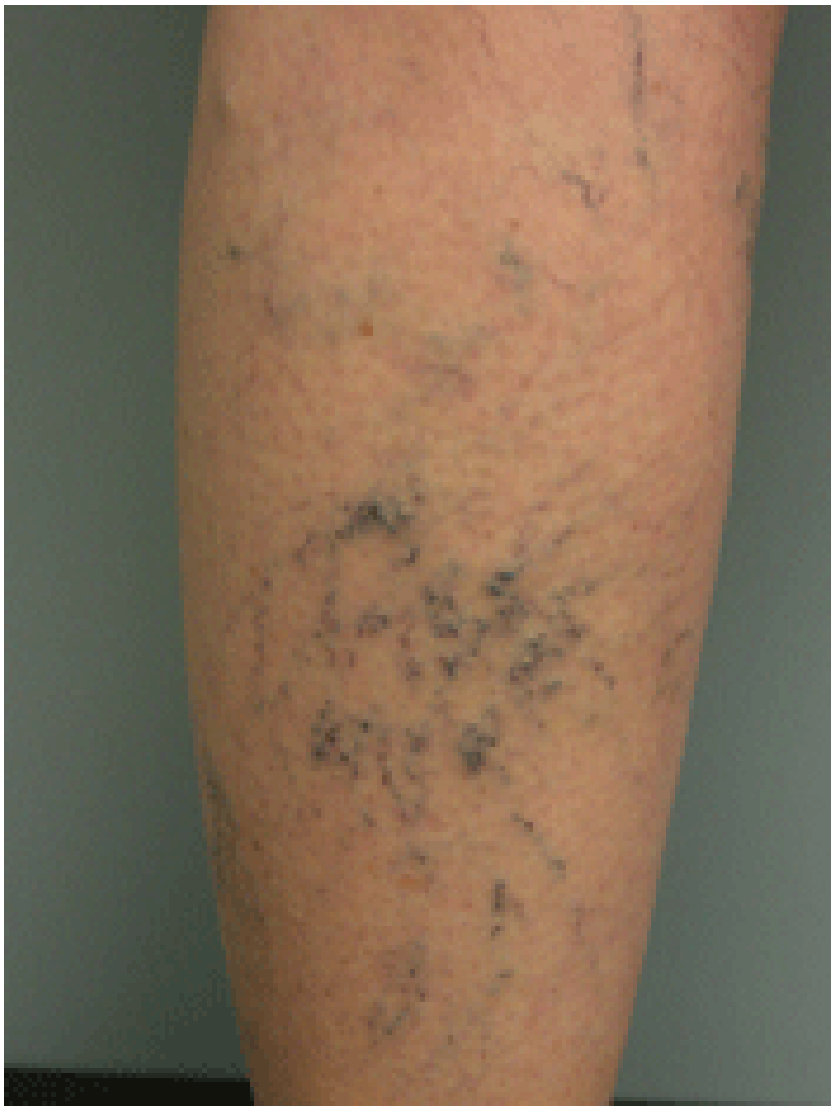

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FIGURE 1.9 C2 VARICOSE VEINS

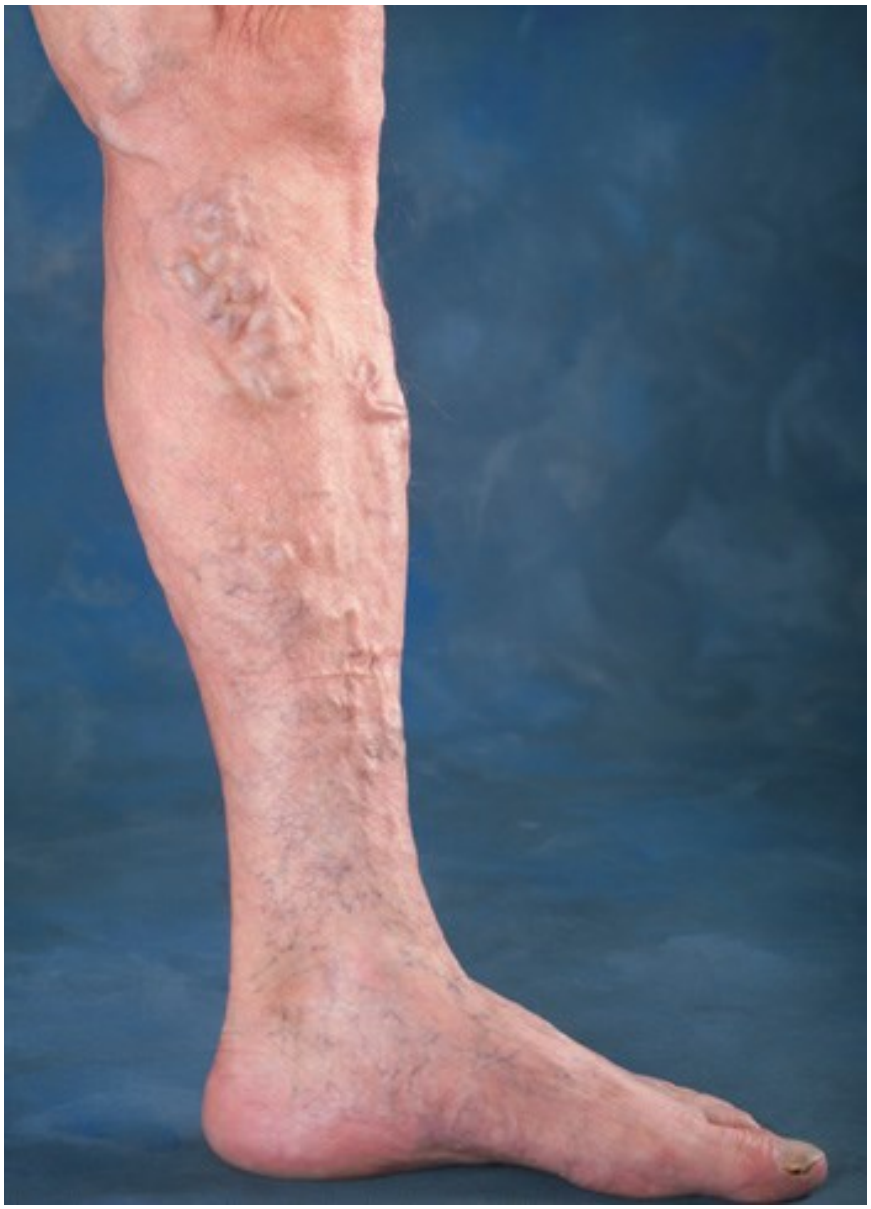

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FIGURE 1.10 C3 CORONA PHLEBECTATICA

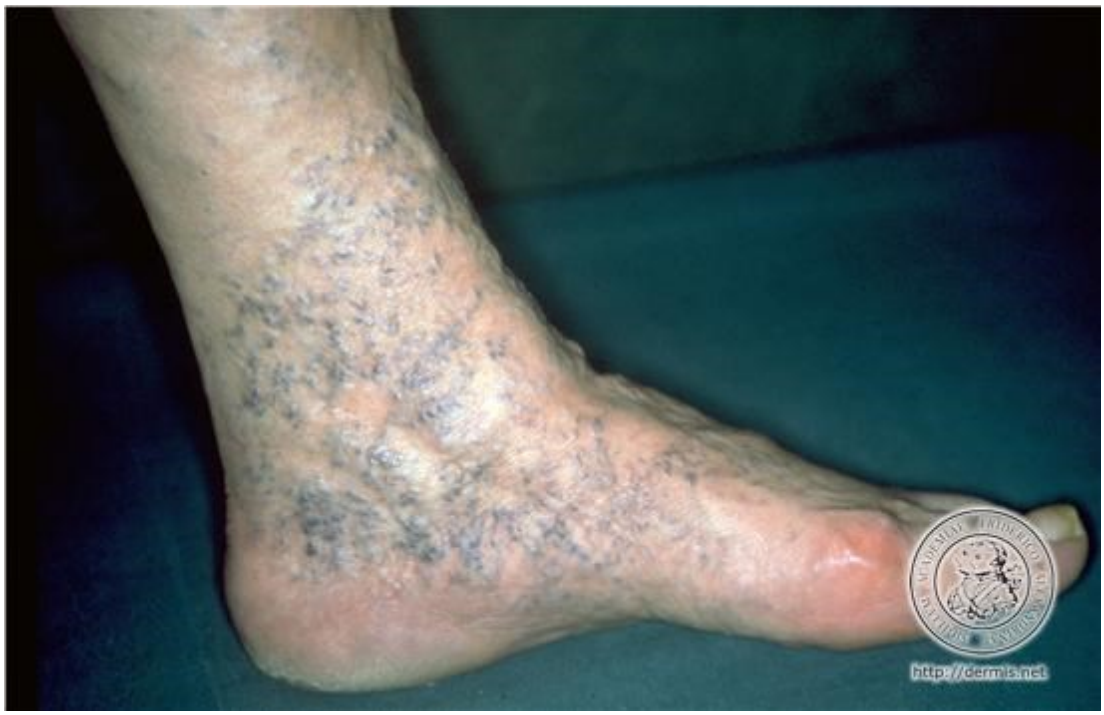

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FIGURE 1.11 C3 OEDEMA

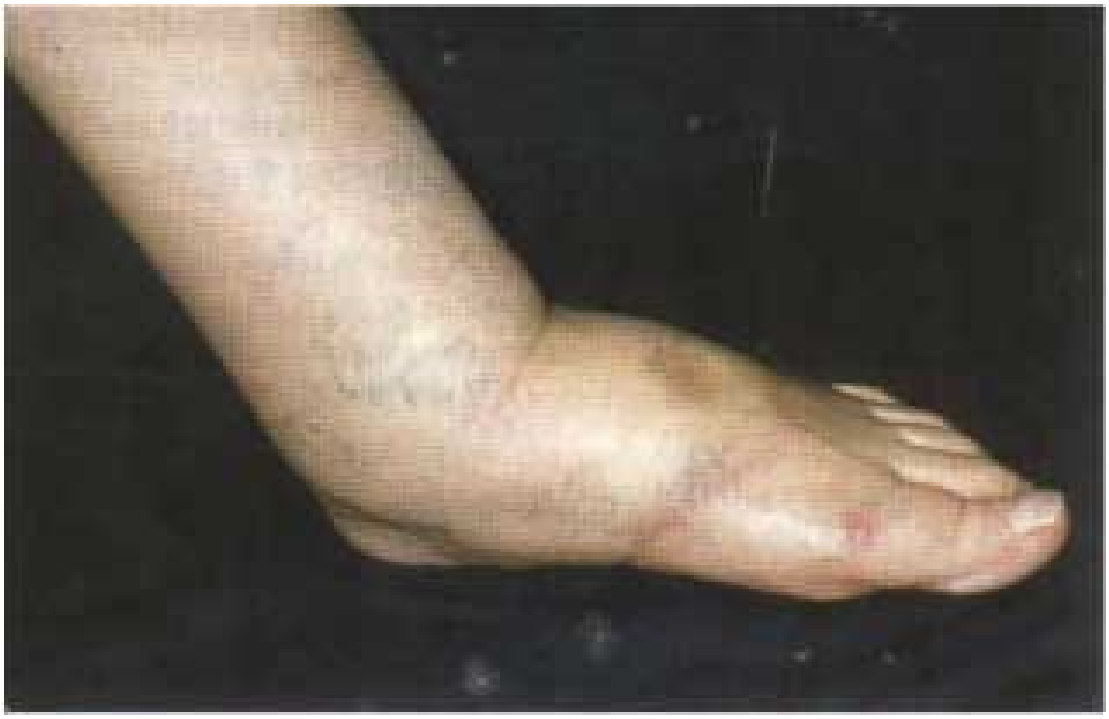

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FIGURE 1.12 C4a PIGMENTATION

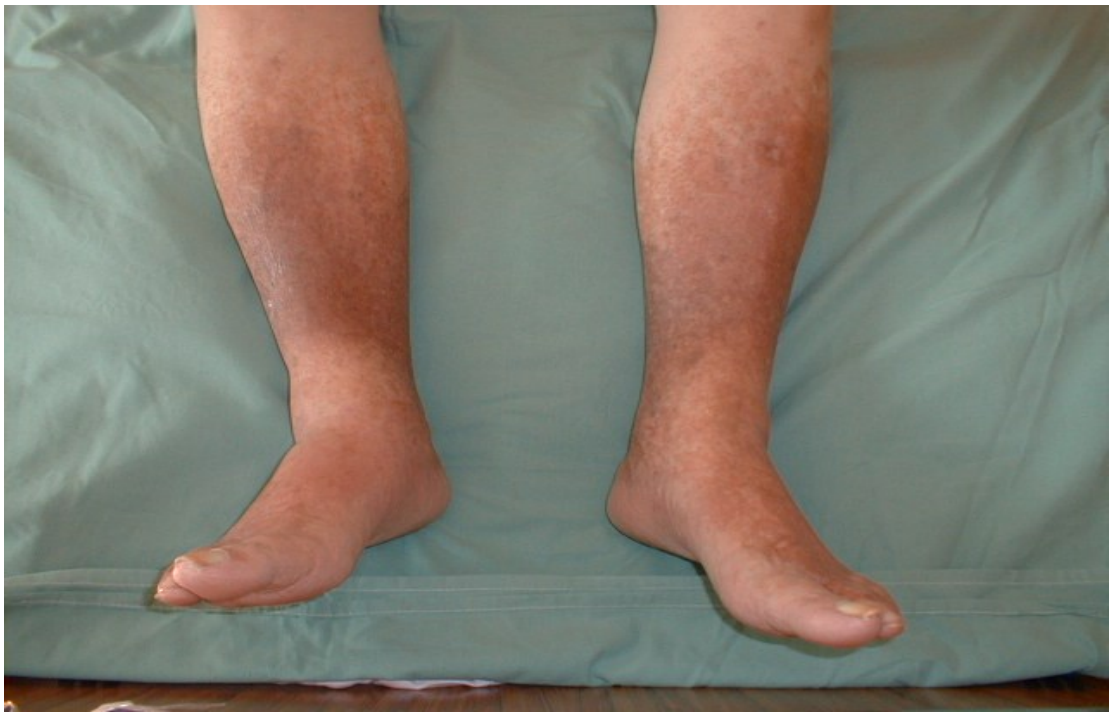

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FIGURE 1.13 C4a VENOUS ECZEMA

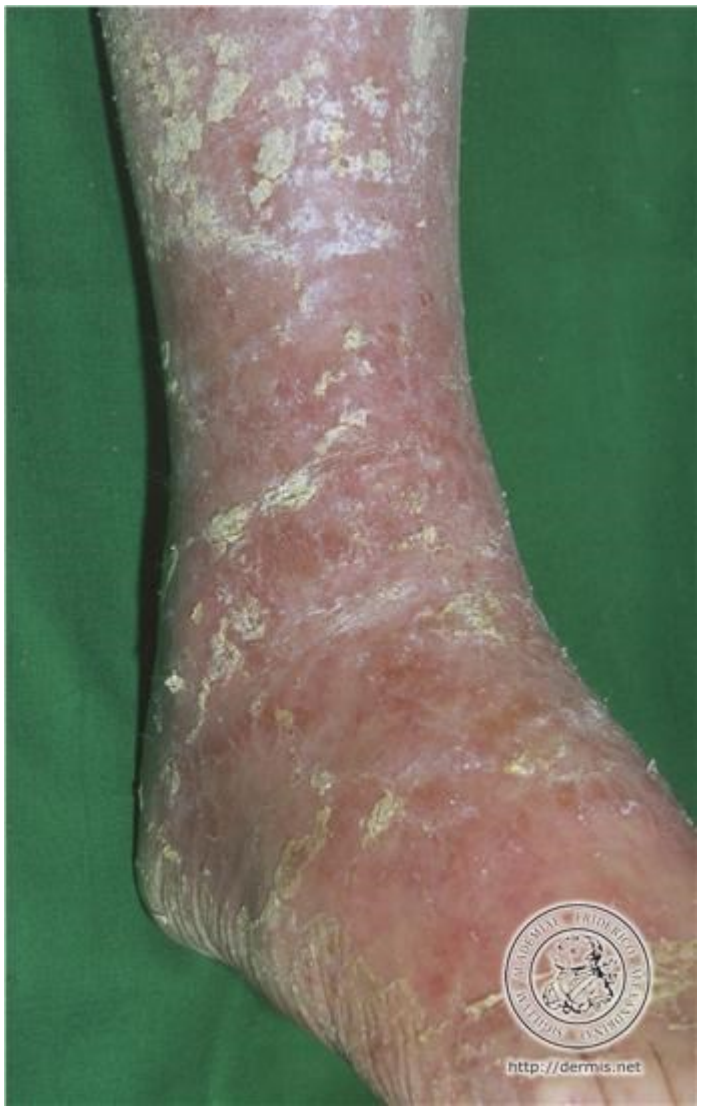

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FIGURE 1.14 C4b LIPODERMATOSCLEROSIS

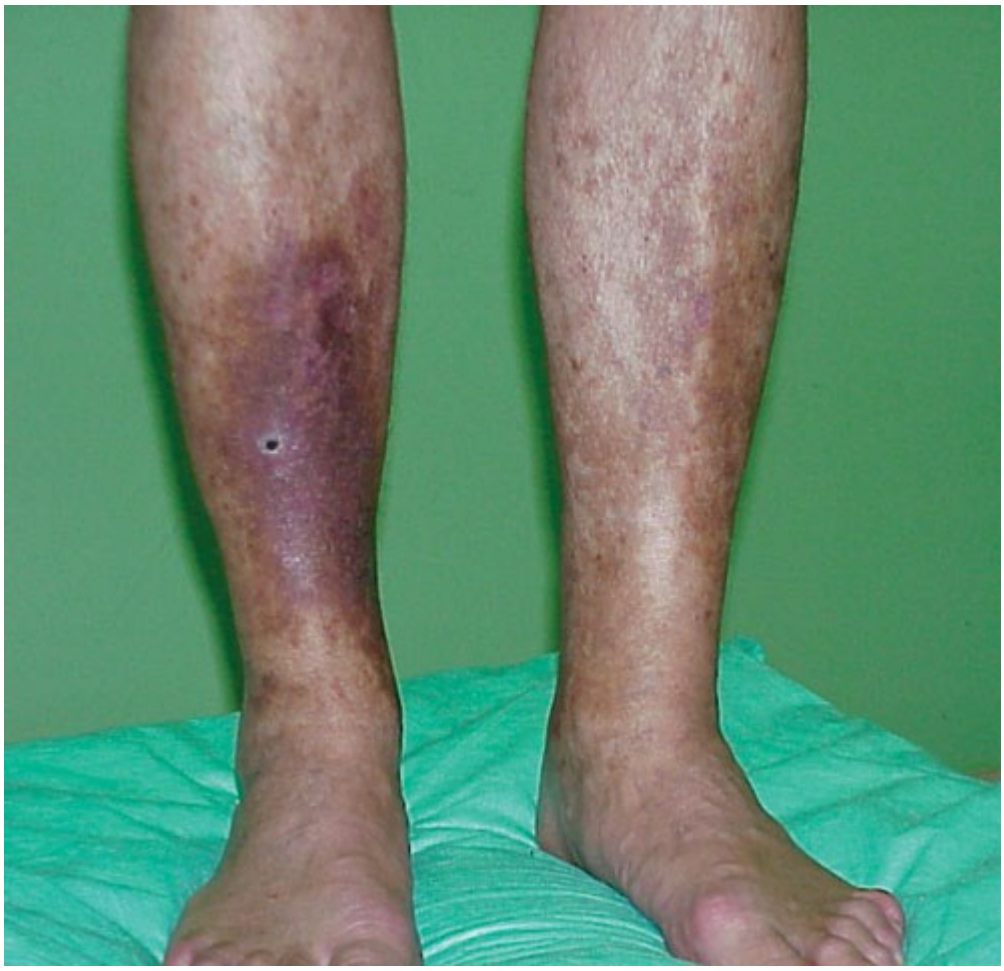

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FIGURE 1.15 C4b ATROPHIE BLANCHE

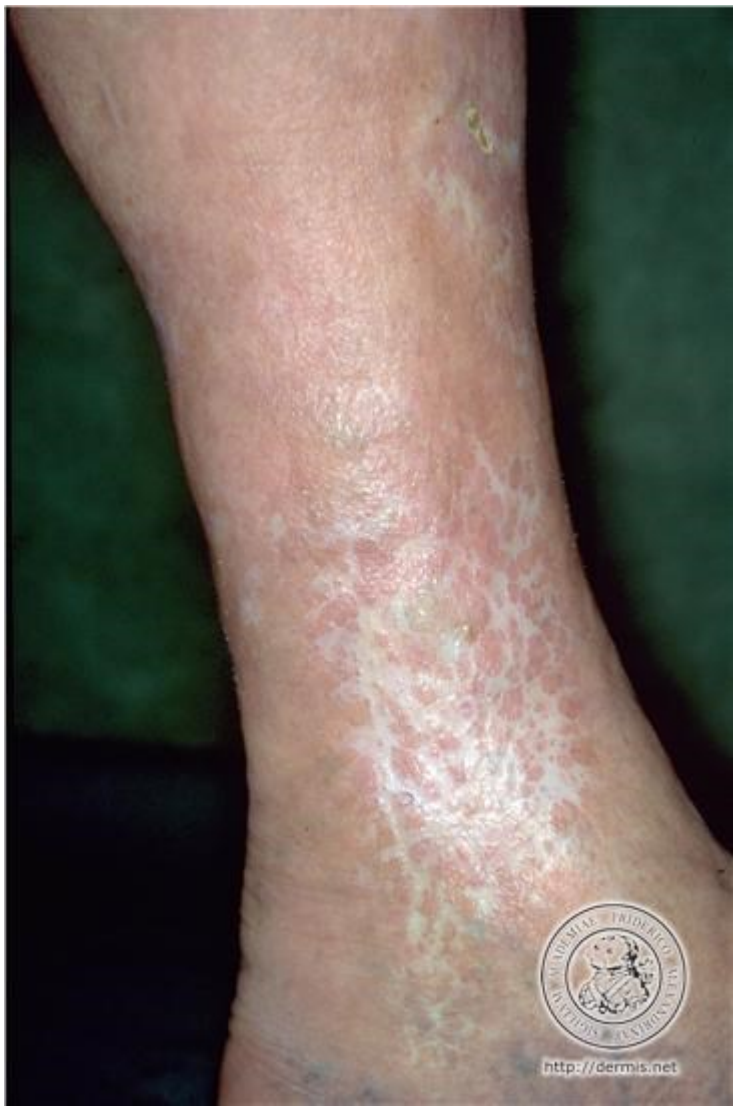

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FIGURE 1.16 C5 HEALED VENOUS ULCER

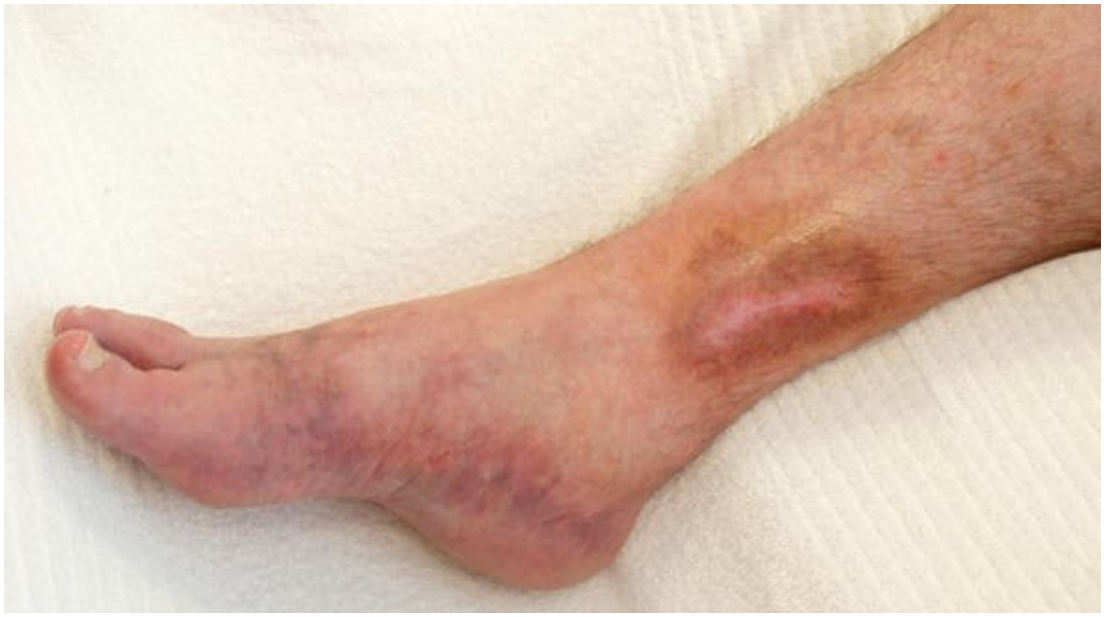

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FIGURE 1.17 C6 ACTIVE VENOUS ULCER

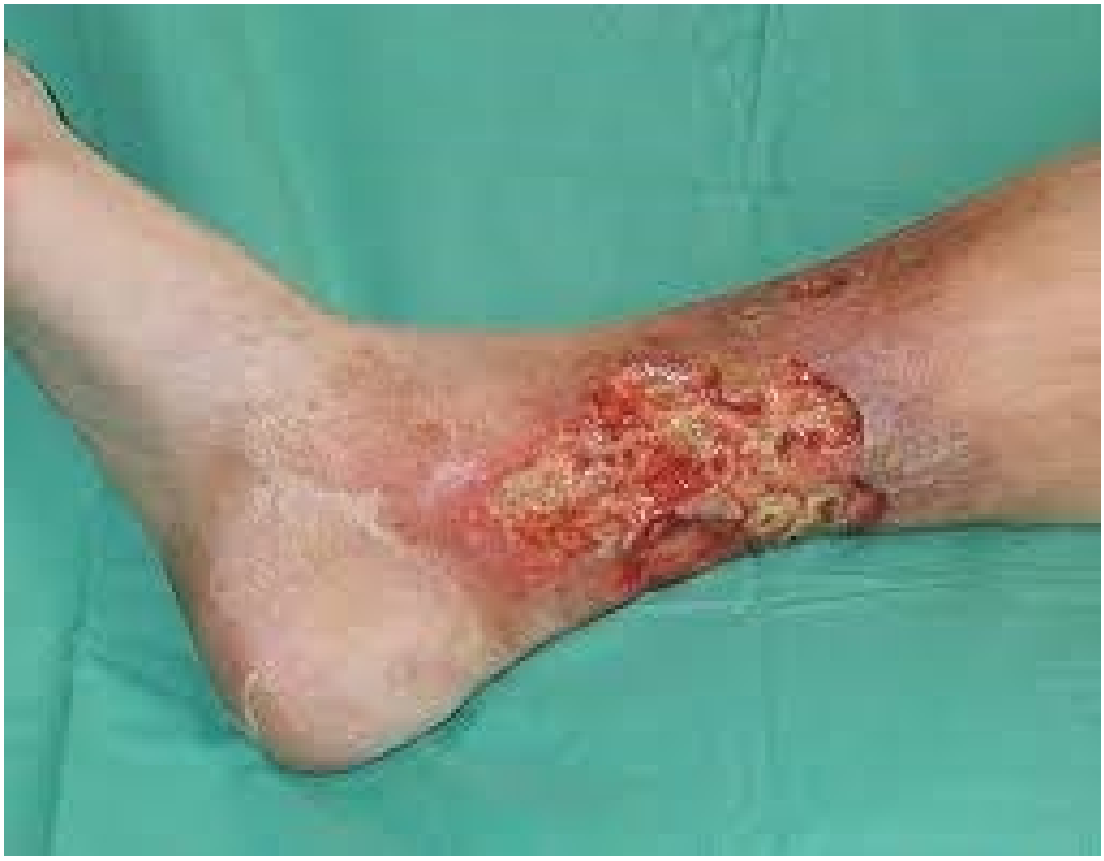

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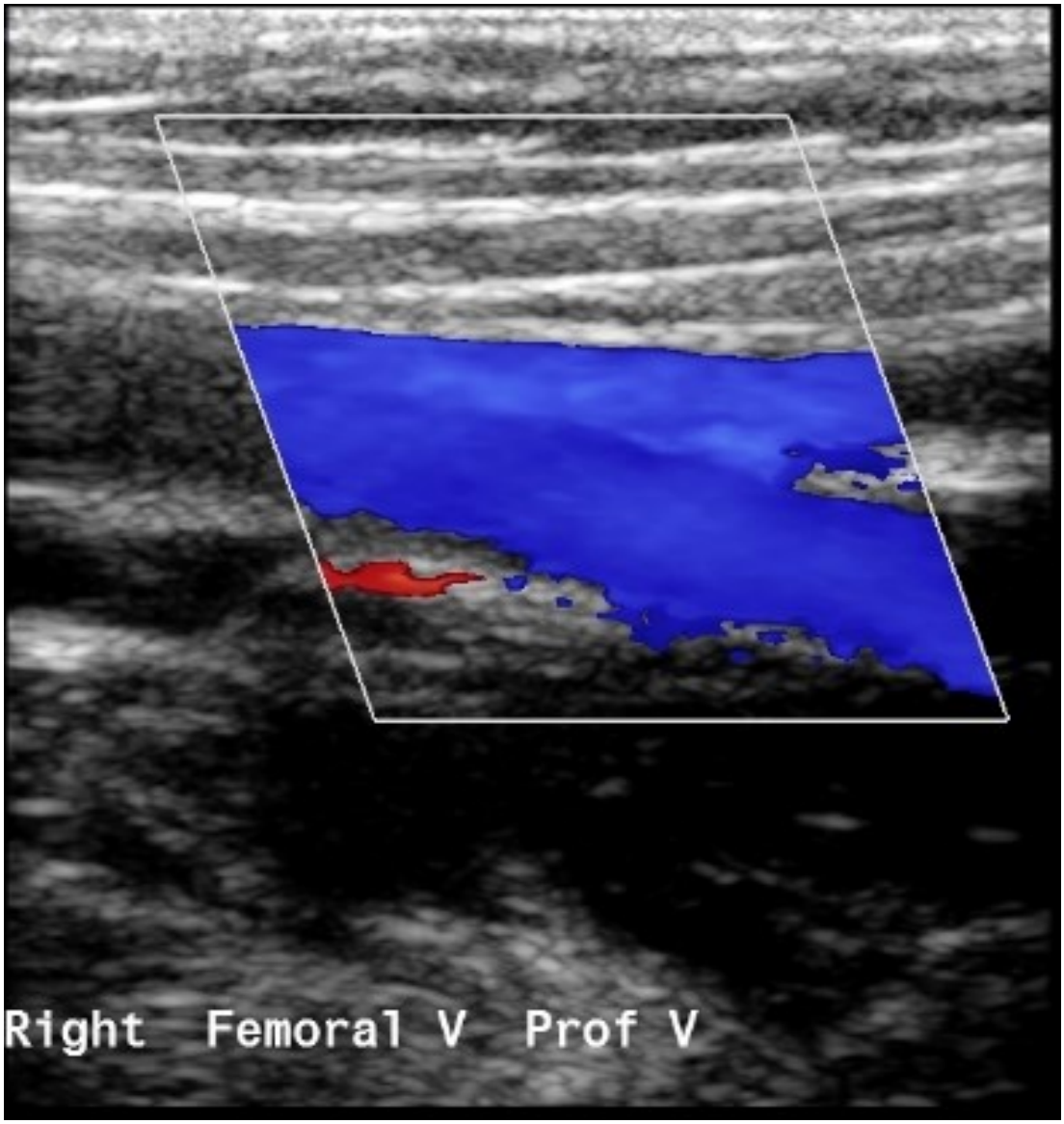
FIGURE 1.18 COLOUR FLOW DUPLEX ULTRASOUND IMAGE



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CHAPTER 2: LITERATURE REVIEW

2.1 CHAPTER OUTLINE

This chapter reviews the available evidence from the literature on the epidemiology of CVD. Firstly the search strategy used to retrieve relevant will be briefly outlined. The prevalence of C2 varicose veins and C3-C6 chronic venous insufficiency from various studies will then be reviewed and variations according to age, gender and race discussed. Evidence on proposed risk factors for C2 varicose veins and C3-C6 CVI will also be summarised.

2.2 SEARCH STRATEGY

A literature search was conducted. Electronic databases searched included Medline, Embase, Cinahl and Current Contents. Keywords used included "*varicose veins*", "*chronic venous insufficiency*", "*chronic venous disease/disorder", "venous ulceration",* "*venous reflux*" and "*risk factors*". In addition, the reference lists of articles were hand searched for relevant studies. Various health services research resources such as NHS, National Institute for Clinical Effectiveness (NICE), Scottish Intercollegiate Guidelines Network (SIGN), Health Technology Assessment (HTA), and the Cochrane Library were consulted via the internet.

2.3 VARICOSE VEINS

2.3.1 Prevalence of varicose veins

The prevalence of varicose veins ranges from 2% to 57% in men and from <1% to 68% in women [Table 2.1]. This variation can be partly explained by differences in the study samples in terms of age, gender and race. In the majority of studies, a minimum age of 15-18 years was used, although one study included children of 10 years (Coon 1973). Some used specific age groups (Carpentier 2004, Ducimetiere 1981, Kontosic 2000, Laurikka 1993, Leipnitz 1989) while two only included patients over 60 years old (Canonico 1998, Komsuoglu 1994). Many used selected populations such as occupational groups (Ducimetiere 1981, Guberan 1973, Hirai 1990, Malhotra 1972, Mekky 1969, Sam 2007, Stvrtinova 1991), or of hospital patients (Franks 1992, Hirai 1990, Jawien 2003, Komsuoglu 1994, Maffei 1986, Pospíšilová 2008, Richardson 1977). Some studies completed in New Guinea (Stanhope 1975) or Tanzania (Richardson 1977) may not be generalisable to the wider population.

Population surveys including the whole study population or a stratified random sample, are considered to be the most accurate method of measuring the true prevalence of a disease (Petrie 2000). If the sample is representative, generalisations can be made in relation to the wider population (Bowling 1997). To date, fifteen general population surveys of varicose veins have been conducted (Abramson 1981, Canonico 1998, Carpentier 2004, Chiesa 2005, Coon 1973, Criqui 2003, Evans 1999, Franks 1992, Komsuoglo 1994, Jawien 2003, Laurikka 2002, Preziosi 1999, Rabe 2003, Sisto 1995, Widmer 1978). Table 2.2 compares the prevalence from these surveys by study sample, method of diagnosis and definition of varicose veins.

Four surveys used self-administered questionnaires to determine the prevalence of varicose veins. Three of these relied on the participant's own observations (Franks 1992, Komsuoglo 1994, Laurikka 2002). Self-diagnosis of varicose veins is a method of data collection proven to be prone to error (Krijnen 1997, Weddell 1969). The fourth was based on the participant's report of a previous diagnosis of varicose veins made by a doctor (Sisto 1995). The prevalence in this study was 6.8% in men compared to 24.6% in women. The significantly lower prevalence observed in men could be due to the fact that they may be more reluctant to consult their doctor about varicose veins.

In the other eleven surveys, patients were examined for the presence of varicose veins (Abramson 1981, Canonico 1998, Carpentier 2004, Chiesa 2005, Coon 1973, Criqui 2003,, Evans 1999, Jawien 2003, Preziosi 1999, Rabe 2003, Widmer 1978). Three of these surveys were conducted before the introduction of the CEAP classification and the prevalence ranged from 10-56% (Abramson 1981, Coon 1973, Widmer 1978). These estimates may be less precise due to the lack of uniform measurement of varicose veins. In the seven surveys that used the C2 CEAP definition of varicose veins, the prevalence was more constant, ranging from 10-39% in men and 15-50% in women (Carpentier 2004, Chiesa 2005, Criqui 2003, Evans 1999, Jawien 2003, Preziosi 1999, Rabe 2003). One survey did not used CEAP to measure varicose veins, but instead defined them as "any reticular or truncal visible varicosity" (Canonico 1998). As reticular veins are classified as C1 according to CEAP, the results of this study are not comparable with other studies which used the C2 CEAP definition of varicose veins. Furthermore, as reticular veins are relatively common in the general population, their inclusion could have resulted in an over estimation of the true prevalence of C2 varicose veins.

2.3.2 Prevalence of varicose veins by age

Evidence on the association between age and varicose veins is relatively conclusive, as the majority of studies suggest that the prevalence increases with increasing age (Abramson 1981, Arnoldi 1958, Canonico 1998, Carpentier 2004, Chiesa 2005, Coon 1973, Criqui 2003, Evans 1999, Franks 1992, Guberan 1973, Hirai 1990, Komsuoglu 1994, Laurikka 1993, Malhotra 1972, Mekky 1969, Novo 1988, Preziosi 1999, Sadick 1992, Sisto 1995, Stvrtinova 1991, Weddell 1969).

At baseline in the Edinburgh Vein Study, the overall prevalence of C2 varices increased from 11.5% in 18-24 year olds to 55.7% in those aged 55-64 years (p=0.001) (Evans 1999). The San Diego population study reported a prevalence of 16.9% in subjects aged less than 50 years which rose to 29.9% in subjects aged over 70 years (Criqui 2003). In a population study with a random sample of 1,319 men and women aged over 65 years, the prevalence of varicose veins did not increase significantly beyond this age (p=0.75) (Canonico 1998).

2.3.3 Prevalence of varicose veins by gender

Many studies have shown that varicose veins are more common in women than in men (Abramson 1981, Arnoldi 1958, Beaglehole 1975, Canonico 1998, Carpentier 2004, Coon 1973, Criqui 2003, Franks 1992, Jawien 2003, Komsuoglu 1994, Kontosic 2000, Laurikka 1993, Leipnitz 1989, Maffei 1986, Novo 1988, Pospíšilová 2008, Preziosi 1999, Rabe 2003, Sisto 1995, Weddell 1969) [Tables 2.1 and 2.2]. In a population-based study in Italy, the prevalence of was twice as high in women as in men (p<0.0001) but only participants aged over 65 years were included in the study (Canonico 1998).

Selection bias may have occurred in some of these studies. Aesthetically, women may be more aware of their varicose veins than men and may consider them to be more of a problem for cosmetic reasons. Consequently, women may be more likely to participate in varicose vein research. It is also important to consider than many of the results from these studies have not been adjusted for age, pregnancy and hormonal factors.

There are several studies which found a higher prevalence in men. In the Edinburgh Vein Study, the age-adjusted prevalence of trunk varices in men was 40% compared to 35% in women ($p=0.01$). In the Bochum Study, by the age of 18-20 years, the male schoolchildren had a higher prevalence of varicose veins than females (Schultz-Ehrenburg 1992). However statistical tests of significance were not reported for these results.

In addition to selection bias, methods of assessing varicose veins may also introduce bias in prevalence figures. Studies relying on self-assessment (Franks 1992, Komsuoglu 1994, Laurikka 1993) or previous diagnosis by a doctor (Sisto 1995) may have under-reported the prevalence in men, as they may be less likely to report varicose veins or consult their doctor about them than women. This hypothesis is supported by findings from the baseline Edinburgh Vein Study (Evans 1999). Prior to examination, only 10% of men reported a previous diagnosis of varicose veins made by a doctor compared with 17% of women, despite the fact that men were subsequently found to have a significantly higher prevalence of varicose veins on examination.

2.3.4 Prevalence of varicose veins by race

Geographical variations in the prevalence of varicose veins suggest a possible correlation with race [Table 2.1]. Several studies demonstrate that varicose veins are rare in Africa compared with Western countries (Abramson 1981, Richardson 1977, Stanhope 1975). A study in Jerusalem found that men born in North Africa had a significantly lower age-adjusted prevalence than immigrants from Europe, America and Israel (Abramson 1981). Another study comparing female cotton workers in England and Egypt observed a significantly increased prevalence in English women compared with Egyptian women (Mekky 1969). In Brazil, a large study of 1,755 participants diagnosed using the Basle classification system, showed a significantly higher prevalence of varicose veins in Caucasians than non-Caucasians (Maffei 1986). Other variations include a higher prevalence in railroad workers from the South compared to the North of India (Malhotra 1972) and a lower prevalence in women of Southern Europe compared with Northern Europe (Guberan 1973). This finding was contradicted by the 24-cities Cohort Study in Italy where the prevalence of varicose veins was 26% in Northern Italy compared to 42% in Southern Italy (Chiesa 2005).

Authors have suggested a possible etiologic role of lifestyle or behavioural patterns in the countries of origin. Ethnic or social factors, diabetes, the habit of sitting in a chair and food fibre intake are other contributing factors proposed in the relationship between race and prevalence of chronic venous disease.

2.3.5 Incidence of varicose veins

The incidence of varicose veins refers to the development of new cases over a period of time in a population initially free of disease. Few studies have measured the incidence of varicose veins. The Framingham Study was a longitudinal study that followed up men and women living in Framingham, USA (Brand 1988). Every two years from 1966 over a 16-year period, participants were examined for varicose veins, defined as 'the presence of distended and tortuous veins, clearly visible on the lower limbs with the subject standing'. Over the 16 years, 396 of 1720 men and 629 of 2012 women initially free of disease developed varicose veins. On average, the two-year incidence rate of varicose veins was 39.4 per 1000 for men and 51.9 per 1000 for women.

The Bochum study in Germany examined schoolchildren on three occasions over an 8 year period (Schultz-Ehrenburg 1992). At the first examination, none of the children aged 10-12 years, had trunk varices, although there was already venous reflux present in the great and small saphenous veins in 2.5% of the children on Doppler examination. At age 14-16 years, 1.7% of the children had trunk varices and 0.8% had varices of the tributary veins while 12.3% had saphenous reflux. This prevalence of trunk and tributary varices increased to 3.3% and 5.0% by age 18-20 years, with a prevalence of 19.8% for saphenous reflux on Doppler examination. The Bonn Vein Study examined 1,978 participants and the incidence of C2 varices was 13.7% over the 6.6 year follow up (Rabe 2010)

2.4 C3-C6 CHRONIC VENOUS INSUFFICIENCY

2.4.1 Prevalence of CVI

There have been many studies on the prevalence of leg ulceration and several on CVI. The sex-stratified estimates of prevalence of CVI in different studies, is presented in Table 2.3. The wide variation in prevalence may be due to the different sampling methods, ages of the sample population, and definitions of chronic ulceration.

2.4.2 Prevalence of CVI by age

Evidence suggests that the prevalence of CVI increases with age. At baseline in the Edinburgh Vein Study, the prevalence of CVI increased linearly with age for both sexes (Evans 2002). The prevalence of all CVI was 25% (95% CI 19.3-31.6) in men and 12.3 (95% CI 8.2-17.2) in women aged 55-64 years ($p<0.001$). In a cross-sectional study of a multi-ethnic sample of 2,211 men and women in San Diego, Criqui et al, reported the prevalence of trophic skin changes in all subjects < 50 years, 50-59 years, 60-69 years and ≥70 years were 2.3%, 4.0%, 8.8% and 10.2%, respectively (Criqui 2003). In a case-control study, Scott et al observed a 6% increase in risk of CVI per one year increase in age (OR 1.1, 95% CI 1.0-1.1) (Scott 1995). In Tecumseh, USA the prevalence of venous-related oedema and skin changes increased from 1.8% in women aged 30-39 years to 20.7% in women over 70 years of age (Coon 1973).

2.4.3 Prevalence of CVI by gender

While the occurrence of varicose veins is usually reported to be more common in women, results with respect to CVI have been inconsistent [Table 2.3]. The prevalence appears to vary according to the severity of disease. For stage C3 including corona and oedema, three studies (Carpentier 2004, Chiesa 2005, Rabe 2003) reported a higher prevalence in woman. For C4 trophic skin changes including eczema and lipodermatosclerosis, the prevalence was higher in women three studies (Coon 1973, da Silva 1974, Komsuoglu 1994) but higher in men in five studies (Carpentier 2004, Chiesa 2005, Criqui 2003, Rabe 2010, Widmer 1978). Gender differences on prevalence for healed and active venous ulceration were conflicting with six studies reporting a higher prevalence in men (Carpentier 2004, Chiesa 2005, Coon 1973, Criqui 2003, da Silva 1974, Franks 1992), two studies reporting a higher prevalence in women (Arnoldi 1958, Komsuoglu 1994) and two reporting no difference in prevalence by gender (Rabe 2010, Widmer 1978). At the baseline stage of the Edinburgh Vein Study, the prevalence of CVI was higher in women up to 45 years of age and then was more frequent in men (Evans 2002). Among those aged 55-65 years, the overall prevalence of CVI in men was double that in women (25.3% versus 12.3%, $p<0.001$). In Tecusmeh, USA, 37% of women and 3.0% of men had skin changes (Coon 1973). The marked gender difference was not demonstrated by the Edinburgh Vein Study which found that 1.1% of women and 1.3% of men had skin changes

2.4.4 Incidence of CVI

Very little research has been done on the incidence of CVI in healthy populations. The Bonn Vein Study II examined 1978 participants after a 6.6 year follow up and reported an incidence of 13.0% for CVI (Rabe 2010). However authors do not stipulate the class of CVI nor how the incidence was measured. It is unclear if the incidence was based on participants free of C2 varices or C3-C6 CVI at baseline. It is important to know if a participant in this study who had C3 CVI at baseline but progressed to C4 CVI at follow up, was included in this incidence calculation. Such an example is a measure of disease progression rather than incidence.

2.5 RISK FACTORS FOR VARICOSE VEINS AND CVI

Predisposing factors for venous disease are difficult to establish due to the interplay of environmental and genetic elements. Consequently the question over whether varicose veins are due to an inherited defect or to some environmental influence remains. Family history of venous disease and pregnancy may both be factors in the development of varicose veins. A case also exists for the role of weight. Aggravating factors such as diet and long hours spent standing have been emphasised. These risk factors will now be discussed.

2.5.1 Family history

There is a general consensus that defective valves are the cause of varicose veins. This can be an inherited problem where people are born with too few valves or valves that do not function properly. Others can be born with abnormalities of the vein wall causing the valves to separate and become leaky.

Several studies have reported that the risk of varicose veins is higher in those with a family history of venous disease (Carpentier 2004, Cornu-Thenard 1994, Criqui 2007, Dindelli 1993, Hirai 1990, Komsuoglu 1994, Kröeger 2004, Laurikka 2002, Lee 2003, Mekky 1969, Sadick 1992, Schultz-Ehrenburg 1992, Scott 1995, Stvrtinova 1991, Weddell 1969) [Table 2.4].

Two studies examined family members to clinically diagnose varicose veins (Cornu-Thenard 1994, Weddell 1969). One study examined 134 families: 67 varicose veins cases and their parents, and 67 controls and their parents (Cornu-Thenard 1994). In total, 402 participants were examined for varicose veins defined as "the presence of a permanent dilatation of a subcutaneous vein of the lower limb visible and tortuous". The prevalence of varicose veins was 90% in those with a history of varices in both parents, 25% in males and 62% in females with one parent affected, and 20% in those with no family history. Only 76 families were included in the second study and it is probably too small to draw any meaningful conclusions (Weddell 1969).

The remaining studies relied on self-reporting of family history. In the Edinburgh Vein Study, the odds ratios for varicose veins were 1.5 (95% CI 1.0-2.3) in men and 2.2 (95% CI 1.4-3.4) in women with a positive family history (Lee 2003). Three other large cross-sectional studies reported higher odds ratios. Carpentier et al. studied 835 participants and measured odds ratios of 3.5 (95% CI 1.9-6.5) and 3.5 (95% CI 2.4-5.1) for men and women respectively (Carpentier 2004). In the San Diego Population Study of 2,211, the odds ratios were 2.9 (95% CI 1.8-4.6) in men and 2.3 (95% CI 1.8-3.1) in women (Criqui 2007). Finally The Tampere Study estimated an odds ratio of 4.9 (95% CI 4.2-5.7) for varicose veins in those with a family history of venous disease (Laurikka 2002)

In a study of 541 Japanese women, 42% of subjects with varicose veins reported a positive family history compared with just 14% of women without disease (Hirai 1990). However, this difference diminished with increasing age. Another study reported that patients with varicose veins were 21.5 times more likely to report a positive family history compared with controls (p=0.0001) (Scott 1995). A study in the Czech republic reported that 87% of varicose veins patients had a positive family history of venous disease (Pospíšilová 2008). However, participants in this study were patients at a phlebology clinic and were selected on the basis that they had varicose veins. There was no control group.

There is less evidence regarding family history and CVI and it is inconsistent. One study reported an odds ratios of 7.2 (95% CI 4.6-11.0) in men and 7.7 (95% CI 5.9-9.9) in women for CVI with a positive family history (Gourgou 2002). A case-control study of 102 cases with venous ulcer and 200 controls with no ulcer reported that family history of maternal venous insufficiency was a risk factor for venous ulcer (adjusted OR 6.9, 95% CI 1.9-24.3) but paternal history was not (adjusted OR 1.2, 95% CI 0.5-2.9) (Bérard 2002). Interestingly the case-control study by Scott et al. which reported a high risk for varicose veins, showed no association between family history and CVI (Scott 1995).

The results of studies relying on self-reported family history must be interpreted with caution. Varicose veins are a common problem and therefore, a large proportion of study subjects would report a positive family history. Those with venous disease would probably be more aware of the occurrence of disease among family members than those without disease.

2.5.2 Pregnancy

It has been hypothesised that the increase in intra-abdominal pressure, combined with the direct pressure exerted on the iliac veins by the uterus during pregnancy, obstructs venous return from the leg. Consequently venous valves rupture, reflux develops and varicose veins form (Cordts 1996). However, this has been refuted as the majority of varices appear during the first three months of the pregnancy (McCausland 1939, Mullane 1952, Rose 1986) when the uterus is not large enough. Furthermore, varicose veins often disappear after birth (Evans 1994). Two studies using ultrasound, confirmed that the diameters of competent and incompetent great and small saphenous veins increase significantly during the first trimester of pregnancy ($p<0.001$) but return to baseline values during the postpartum period (Boivin 2000, Cordts 1996).

The association between pregnancy and varicose veins may have a hormonal component. Saphenous veins contain oestrogen and progesterone receptors and although their function is unknown, it has been postulated that the increase in hormones circulating through the blood in pregnancy may cause these receptors to mediate venous dilation and cause valve failure (Masiah 1999). Contrary to this theory, the number of pregnancies in developing countries is far higher than Westernised ones, yet the prevalence of varicose veins is lower in the former. It remains unclear whether pregnancy is an independent risk factor for varicose veins or whether it simply accelerates venous disease in susceptible individuals.

The majority of studies show an association between varicose veins and pregnancy (Abramson 1981, Carpentier 2004, Chiesa 2005, Criqui 2007, Dindelli 1993, Guberan 1973, Hirai 1990, Komsuoglu 1994, Laurikka 2002, Maffei 1986, Mekky 1969, Richardson 1977, Sisto 1995, Stvrtinova 1991, Weddell 1969, Widmer 1978) [Table 2.5]. The Edinburgh Vein Study found no association between pregnancy and varicose veins (Lee 2003). However, in the same study, pregnancy was implicated as a risk factor for venous reflux (Fowkes 2001).

Several studies report that women with at least one pregnancy have a higher prevalence of varicose veins than childless women (Abramson 1981, Carpentier 2004, Chiesa 2005, Dindelli 1993, Komsuoglu 1994, Maffei 1986, Stvrtinova 1991, Widmer 1978). A study of 611 women in Italy reported an age-adjusted odds ratio of 2.0 (95% CI 1.3-2.9) with one or more pregnancies (Dindelli 1993). Three large population-based studies on a total of 7,279 female participants confirmed the association between pregnancy and varicose veins (Carpentier 2004, Chiesa 2005, Widmer 1978). The Basle Study of 2,264 female employees demonstrated a significantly higher age-adjusted prevalence of trunk varices in parous women (Widmer 1978) while in a French study of 558 female participants, the odds ratio of varicose veins was twofold in women with at least one pregnancy compared to nulliparous women (p=0.007) (Carpentier 2004). Finally, in the Italian 24-Cities Cohort Study of 4,457 female participants, the prevalence of varicose veins was 20%, 35% and 50% in women with 0, 3 and 4 pregnancies respectively. Crucially, in these three studies, all patients were examined by a clinician and a standard definition of varicose veins was used.

Evidence also suggests a positive relationship between prevalence of varices and an increasing number of pregnancies (Chiesa 2005, Dindelli 1993, Laurikka 2002, Sisto 1995), although only in one study was the effect independent of age (Sisto 1995). In the Tampere study of 3,101 women, the prevalence of varicose veins with 0, 1, 2, 3, and 4 or more pregnancies were 32%, 38%, 43%, 48%, and 59%, respectively (Laurikka 2002) while in the Mini-Finland Health Survey the odds ratio for varicose veins was 1.4 (95% CI 1.0-1.9) in women with one pregnancy and 3.0 (95% CI 2.3-4.1) in women with five pregnancies (Sisto 1995). However, in both studies, women self-diagnosed varicose veins through a questionnaire and no validation of this method of assessment was performed. The Tecumseh Community Health Study (Coon 1973), the Framingham Study (Brand 1988), and several other studies (Abramson 1981, Hirai 1990, Richardson 1977, Scott 1995) failed to show a rising prevalence with increasing number of pregnancies.

Evidence on the association between pregnancy and CVI is limited. A case control study of 102 cases with venous ulcer and 200 controls without determined that pregnancy was associated with venous ulceration (OR 1.2, 95% CI 1.0-1.5) (Bérard 2002). However the odds ratio was not adjusted for age, a confounding factor in venous leg ulceration. A case-control study by Scott reported that women with CVI had more pregnancies than those with varicose veins but this association disappeared after adjusting for age (Scott 1995).

2.5.3 Oral contraceptives

Very few studies have investigated the effect of oral contraceptives on varicose veins. One case-control study reported that women with varices were more likely to use oral contraceptives than women free of varices (Sadick 1992). In contrast, the Basle Study (Widmer 1978), the Mini-Finland Health Survey (Sisto 1995) and a case-control study in North America (Scott 1995), all reported no association between varicose veins and oral contraceptive use. It should be noted that the oral contraceptive pill was introduced in Switzerland only four years before the Basle Study and therefore the exposure period was very short. A limitation of studies measuring the relationship between oral contraceptives and varicose veins is selection bias. The risk of the pill on venous disorders such as deep vein thrombosis is well known and may influence a woman's decision to participate in the research study.

2.5.4 Hormone replacement therapy

Results of studies on the association between postmenopausal hormone replacement therapy (HRT) and varicose veins are inconsistent. In the Mini-Finland Health Survey the age-adjusted prevalence of varicose veins in women aged over 50 years was 35% in women taking HRT compared with 27% in those not taking it. The result was statistically significant but this survey diagnosed varicose veins by a questionnaire (Krijnen 1997). Two population-based studies investigated the use of HRT but neither found it to be associated with varicose veins (Carpentier 2004, Lee 2003). One population-based study reported that varicose veins developed after the menopause in 38% of 759 female participants (Canonico 1998). However, participants were aged over 65 years at the time of participating in the study and thus recall bias may have occurred.

2.5.5 Obesity

It has been postulated that in obese patients, fat tissue augments surrounding veins thus impeding the normal exchange of blood between deep and superficial veins (Lemaire 1988). One study which measured the cross-sectional area of the saphenofemoral and great saphenous veins, reported significant associations with increased BMI for both veins ($p<0.0001$) (Kröeger 2003). It should be noted that the association was only tested in those with C0 CEAP.

Several studies have shown that BMI is associated with varicose veins. However not all studies showed an association (Dindelli 1993, Hirai 1990). The Basle Study (Widmer 1978), Framingham Study (Brand 1988) and a study of 4,488 participants in Jerusalem (Abramson 1981) all reported a significant association between trunk varices and BMI but no comparable effect in men. In an Italian study, the prevalence of varicose veins increased significantly with BMI for women ($p<0.0001$) but not for men ($p=0.54$) (Canonico, 1998 70 /id). The Edinburgh Vein Study confirmed these findings (Lee 2003). A study of 104 postmenopausal women in Italy found that obesity, measured as BMI > 30 kg/m^2, was significantly associated with varicose veins (OR 5.8, 95% CI 1.2-28.2) after adjusting for age and sex hormones (Iannuzzi 2002). This study also reported that varicose veins were associated with increased hip and thigh circumference ($p = 0.04$) but not waist circumference ($p=0.21$) supporting the theory that excess fat may impact venous circulation in the lower limbs. Since it is unlikely that obesity is a risk factor for one sex and not the other, it may be the case that being overweight merely accelerates the development of varicose veins in individuals already susceptible to the condition.

Additionally, the association was maintained across increasing grades of severity in women. The weight of women with grades 0, I, II and III varicose veins increased linearly from 66kg, 68 kg, 73 kg and 74 kg ($p \leq 0.0001$) while the corresponding BMI also increased linearly from 25, 26, 27 and 28 kg/m2 ($p \leq 0.0001$). However there was no association for height. This is supported by several other studies who found obesity to be a risk factor in women only (Brand 1988, Canonico 1998, Gourgou 2002, Kontosic 2000, Mekky 1969, Sisto 1995). Seidell et al. found that moderately overweight women (BMI = 25.0-29.9 kg/m^2) were more likely to have varicose veins (OR 1.5, 95% CI, 1.2-1.9) than women of a normal weight. Furthermore, obese women (BMI = ≥ 30.0 kg/m^2) were three times more likely to have varicose veins (Seidell 1986). In a female population in Switzerland, although there was an increased prevalence of varicose veins with increasing body weight, the association was not significant after adjusting for age (Guberan 1973)

Evidence suggests that obesity is particularly associated with the more severe forms of varicose veins, especially in women (Brand 1988, Lee 2003, Widmer 1978). However these studies did not adjust for parity and given the fact that parous women tend to have a higher average body weight than nulliparous women, this may have been a confounding factor in the association between obesity and varicose veins.

There are fewer studies on CVI and obesity. One case control study found no association between BMI > 27 kg/m^2 and venous ulceration (Bérard 2002). Scott et all reported an age-adjusted odds ratio of 1.06 kg/m^2 (95% CI 1.0-1.1) for CVI patients versus controls with no venous disease and an age-adjusted odds ratio of 1.07 kg/m^2 (95% CI 1.0-1.1) for CVI patients versus varicose vein patients (Scott 1995)

2.5.6 Mobility at work

Certain occupations, in particular those involving prolonged standing and/or heavy lifting at work, have been proposed as risk factors for varicose veins. Standing for prolonged periods of time results in increased hydrostatic pressure which leads to impeded blood flow and stasis in the leg veins. Increase in pressure can also impair the function of the calf muscle pump, which is important for the venous return of blood. The calf muscle pump does not suffer during walking because of the activation of the leg muscle pump (Krijnen 1997)

Several studies reported that a standing occupation is associated with an increased prevalence of varicose veins (Abramson 1981, Brand 1988, da Silva 1974, Gourgou 2002, Kakande 1981, Lee 2003, Mekky 1969, Pinto 1995, Sadick 1992, Scott 1995, Sisto 1995, Stvrtinova 1991). A few studies however, found no association (Canonico 1998, Guberan 1973, Maffei 1986, Malhotra 1972, Weddell 1969). A community study of 4,488 men and women in Jerusalem, Israel reported an odds ratio of 1.6 for standing at work compared to little standing and the association remained significant after adjusting for age and sex ($p<0.01$) (Abramson 1981). One study found that, while there was no association with standing at work, there was a correlation with heavy lifting. The prevalence of varicose veins was significantly higher in men who lifted heavy objects at work (43%) compared to those who did not (21%). The same was true for women, where the prevalence of varicose veins was 59% in those who lifted heavy objects compared to 33% who did not. Both associations were statistically significant ($p<0.05$).

In the Framingham Study, authors reported that the number of hours spent each day in sedentary activities was significantly associated with the incidence of varicose veins in women (Brand 1988). When incidence rates were adjusted based on type of work that was done, women with four or less hours a day of sedentary activities had a 2-year adjusted incidence rate of varicose veins of 57/1,000. Women with eight or more hours a day of sedentary activity had a 2-year adjusted incidence rate of 74/1,000. In men the differences (44/1,000 and 48/1,000 respectively) were not significant.

One large population-based 12-year follow up study in Denmark analysed hospitalisations due to varicose veins according to ICD and national hospital registers. In total 40 men and 71 women were admitted to hospital requiring treatment for varicose veins. For those who stood for prolonged periods of time (defined as seldom or never sitting) the pooled estimate of the adjusted relative risk was 1.8 (95% CI 1.2-2.7) while adjusted relative risk was 1.7 (95% CI 0.9-3.3) among men and 1.8 (95% CI 1.1-2.9) among women (Tüchsen 2005).

Care should be taking in drawing conclusions from studies on mobility at work given the difficulty in retrospectively ascertaining participants' workplace posture, particularly over many years of work. In the Edinburgh Vein Study, mobility was measured in relation to the amount of time spent sitting, standing, walking or heavy lifting at work. Although standing may be an aggravating factor for venous disease, it is unlikely to be a primary cause. For example, there is no evidence that Africans stand for less time than Europeans, yet the prevalence of venous disease in the former is thought to be considerably less than in the latter.

2.5.7 Physical activity

Physical activity has also been suggested as a risk factor for venous disease due to the functional changes that occur during exercise. The Framingham Study reported that men and women with varicose veins were less physically active than those with no varices (Brand 1988). In contrast, a study of women working in a department store in Slovakia, found no significant association between the prevalence of varicose veins and physical activity levels (Stvrtinova 1991). Conversely, a case-control study carried out in America found that cases with varicose veins reported the highest frequency of exercise compared with a control group with no varices but this association diminished after adjusting for age (Scott 1995). It is important to consider that the presence of distended varicose veins are often painful and thus may influence the level of activity chosen by the individual. As such, physical activity levels may have diminished as a result of this rather than the lack of physical activity causing the initial varicosity.

One case control study of 102 cases with venous ulcers and 200 controls reported an odds ratio of 8.9 (95% CI 1.1-72.0) for ulceration in people who had engaged in vigorous exercise (e.g. running, football squash). The odds ratio was not adjusted for age but given that the prevalence of leg ulceration is increased in older people who are less likely to engage in strenuous physical activity, this is an unexpected finding. Physical activity was ascertained for a 20-year period before the study. There are always difficulties in measuring exercise levels over such a long period. Furthermore, study participants may feel like they are being judged and therefore over-report their exercise levels.

2.5.8 Diet

A diet deficient in fibre-rich foods has been proposed as a risk factor for varicose veins. It is considered that the lack of fibre causes constipation and the subsequent straining to pass a stool, produces an increase in intra-abdominal pressure which, over a period of time, causes the leg veins to dilate and changes to occur in the superficial or deep venous system (Burkitt 1972). Another theory is that an overloaded colon could press on the iliac veins and obstruct venous return from the legs (Cleave 1959)

Few studies have examined the dietary habits and most are of limited use because they often make no allowance for confounding factors. Constipation was found to be a positive risk factor among a study of Sicilian people (Novo 1988). However, in an Israeli population, constipation was shown to have only a weak association with varicose veins in women and no association in men. Two studies found no association (Canonico 1998, Mekky 1969). Results from the Edinburgh Vein Study showed an increased risk of saphenous trunk varices in men who reported that they strained at the initiation of a bowel movement (Lee 2003) . In women, there was a suggestion of an inverse relationship. However, fibre intake was unrelated to the prevalence or severity of varicose veins in men and women.

2.5.9 Smoking

Smoking leads to a decrease fibrinolytic activity which has been suggested as a possible mechanism for changes in the vein walls (Browse 1977, Cleave 1960). In the Aachen study, increased viscosity and blood clotting was found in patients with venous disorders compared with those without (Leipnitz 1989).

The Framingham Study noted a correlation between cigarette smoking and varicose veins in men, but not in women (Brand 1988). Similarly, a study on French male employees (Ducimetiere 1981), a German cohort study (Leipnitz 1989), and an American case-control study (Scott 1995) all reported a positive association. In a study by Scott, the association with years smoked diminished after adjusting for age. However, not all studies found an association (Abramson 1981, Canonico 1998, Carpentier 2004, Franks 1992, Hirai 1990, Komsuoglu 1994, Lee 2003). Indeed a cross-sectional study in Finland study showed that varicose veins were less prevalent in women who smoked (Sisto 1995). Furthermore, a German study indicated a protective effect of smoking in both genders (Kröeger 2004).

A case-control study in France analysed the effect of smoking in 1,806 cases with lower limb venous insufficiency, matched by gender and in 10-year age bands to 1806 controls with no venous insufficiency (Gourgou 2002). After adjusting for other risk factors, results showed a significant association with smoking. The odds ratio for developing venous insufficiency was 1.8 for those who smoked 10-19 cigarettes a day (95% CI 1.4-2.2) and 2.4 for those who smoked 20 or more cigarettes a day (95% CI 1.8-3.1) (both $p<0.001$).

Smoking appeared to have a protective effect on venous ulceration in one case-control study in Canada (Bérard 2002). This association disappeared after adjusting for exercise levels as smokers were less active than non-smokers. However this contradicts the earlier association reported in the same study that vigorous exercise is a risk factor for venous ulceration.

2.5.10 Social class

The finding regarding varicose veins and social class have been inconsistent. One study showed a higher prevalence of varicose veins in the lower social classes (Ducimetiere 1981) whilst others have shown no effect (Scott 1995, Sisto 1995). At baseline in the Edinburgh Vein Study, there was no obvious relationship between social class and the prevalence of trunk varices. The age- and sex-adjusted prevalence was higher in manual workers (social classes IIIM-V) than non-manual workers (social classes I-IIIM) but the difference did not reach statistical significance (Lee 2003) . Other studies have shown that venous disease is related to other socioeconomic measures such as family income and level of education (Abramson 1981, Scott 1995).

2.6 CHAPTER SUMMARY

Although numerous epidemiological studies of CVD have been conducted, the exact prevalence remains difficult to determine. Estimates of the prevalence of varicose veins vary widely due to differences in variability of the study populations including age, race and gender and method of measuring disease. Venous ulceration is less common, affecting approximately 0.3% of the adult population. Very little data is available on the incidence of CVD. A universal finding in epidemiological studies is that the prevalence of CVD increases with age. Evidence on the difference in prevalence between men and women is less conclusive. Family history of CVD and prolonged standing have been proposed as risk factor but both are prone to bias in research studies. Obesity and pregnancy have been suggested but they may be aggravating factors rather than primary causes. Other postulated risk factors include hormonal factors, bowel habit and smoking but evidence is lacking.

TABLE 2.1 PREVALENCE OF VARICOSE VEINS BY SEX IN STUDIES FROM DIFFERENT COUNTRIES

					PREVALENCE	
FIRST AUTHOR	**YEAR [a]**	**LOCATION**	**STUDY SAMPLE**	**SAMPLE SIZE**	**MALE (%)**	**FEMALE (%)**
Arnoldi	1958	Denmark	Clinic attendees aged > 25 years	536	40.7	73.2
Bobek	1966	Bohemia	General population aged > 15 years	15,060	6.6	14.1
Weddell	1966	UK	General population aged > 15 years	289	31.0	36.0
Mekky	1969	Egypt	Female cotton workers aged 15-74 years	467	-	5.8
Mekky	1969	England	Female cotton workers aged 15-74 years	504	-	32.1
Malhotra	1972	India (South)	Male railroad workers aged 18-65 years	323	25.1	-
Malhotra	1972	India (North)	Male railroad workers aged 18-65 years	354	6.8	-
Coon	1973	United States	General population aged > 10 years	6,389	12.9	25.9
Guberan	1973	Switzerland	Female store employees aged ≥ 15 years	610	-	29.0
Beaglehole	1975	Cook Island	General population aged 15-64 years	377	2.1	4.0
Beaglehole	1975	Cook Island	General population aged 15-64 years	417	15.6	14.9
Beaglehole	1975	New Zealand	General population aged 15-64 years	721	33.4	43.7
Beaglehole	1975	Tokelau Island	General population aged 15-64 years	786	2.9	0.8

[a] Year of publication

TABLE 2.1 PREVALENCE OF VARICOSE VEINS BY SEX IN STUDIES FROM DIFFERENT COUNTRIES (CONTINUED)

					PREVALENCE	
FIRST AUTHOR	**YEAR [a]**	**LOCATION**	**STUDY SAMPLE**	**SAMPLE SIZE**	**MALE (%)**	**FEMALE (%)**
Stanhope	1975	New Guinea	Rural villagers aged ≥ 20 years	1,457	5.1	0.1
Richardson	1977	Tanzania	Clinic outpatients aged ≥ 18 years	1,000	6.1	5.0
Abramson	1981	Israel	General population aged ≥ 15 years	4,802	10.4	29.5
Ducimetiere	1981	France	Male employees aged 42-53 years	7,425	26.2	-
Maffei	1986	Brazil	Patients aged > 15 years	1,755	37.9	50.9
Novo	1988	Italy	Villagers	1,122	19.3	46.2
Leipnitz	1989	Germany	Random sample aged 45-65 years	2,821	14.5	29.0
Hirai	1990	Japan	Hospital patients and staff aged ≥ 15 years	541	-	45.0
Stvrtinova	1991	Slovakia	Female workers in a department store	696	-	60.5
Franks	1992	England	General practice patients aged 35-70 years	1,338	17.4	31.6
Laurikka	1993	Tampere, Finland	General population aged 40-60 years	5,568	18.4	41.7
Komsuoglo	1994	Turkey	Hospital patients aged > 60 years	856	34.5	38.3
Sisto	1995	Finland	General population aged 40-60 years	8,000	6.8	24.6

[a] Year of publication

TABLE 2.1 PREVALENCE OF VARICOSE VEINS BY SEX IN STUDIES FROM DIFFERENT COUNTRIES (CONTINUED)

					PREVALENCE	
FIRST AUTHOR	**YEAR [a]**	**LOCATION**	**SAMPLE TYPE**	**SAMPLE SIZE**	**MALE (%)**	**FEMALE (%)**
Krijnen	1997	The Netherlands	Male employees with a standing occupation	387	58.0	-
Canonico	1998	Italy	Random sample aged > 65 years	1,319	17.0	35.2
Evans	1999	Edinburgh, Scotland	General population aged 18-64 years	1,566	39.7	32.2
Preziosi	1999	France	SUVIMAX cohort participants aged 35-60 years	3,065	10.8	18.1
Kontosic	2000	Croatia	Working population	1,324	18.9	34.6
Criqui	2003	San Diego, USA	University staff aged 40-79 years	2,211	15.0	27.7
Rabe	2003	Bonn, Germany	General population aged 18-79 years	3,072	12.4	15.8
Jawien	2003	Poland	Clinic outpatients aged 16-97 years	40,095	28.0	35.0
Carpentier	2004	France	General population aged 42-53 years	8,000	30.0	51.0
Sam	2007	UK	Asian men attending mosque, mean age 67 years	100	33.0	-
Pospíšilová	2008	Czech Republic	Phlebology clinic patients aged 16-80 years	319	36.0	54.0

[a] Year of publication

TABLE 2.2 PREVALENCE OF VARICOSE VEINS BY SEX FROM SURVEYS OF THE GENERAL POPULATION

AUTHOR [a]	YEAR [b]	LOCATION	SAMPLE SIZE	AGE [c]	VARICOSE VEIN DEFINITION	DIAGNOSIS [d]	PREVALENCE (%)	
							MALE	FEMALE
Coon	1973	USA	6,389	> 10	Prominent superficial veins in the lower extremities	Examination	12.9	25.9
Widmer	1978	Switzerland	4,422	25-74	Dilated subcutaneous veins	Examination	56.0	55.0
Abramson	1981	Israel	4,802	> 15	Distended and tortuous subcutaneous veins, excluding very small veins	Examination	10.4	29.5
Franks	1992	England	1,338	35-70	Asked “Have you ever had large veins or varicose veins in your legs?”	Questionnaire	17.0	31.0
Laurikka	1993	Finland	5,568	40-70	Clearly visible, dilated, tortuous veins of lower extremities	Questionnaire	18.4	41.7
Komsuoglu	1994	Turkey	850	> 60	Dilated, tortuous and elongated veins of the lower extremities	Questionnaire	35.4	38.2

[a] First author
[b] Year of publication
[c] Age in years
[d] Method of varicose vein diagnosis

TABLE 2.2 PREVALENCE OF VARICOSE VEINS BY SEX FROM SURVEYS OF THE GENERAL POPULATION (CONTINUED)

AUTHOR [a]	YEAR [b]	LOCATION	SAMPLE SIZE	AGE [c]	VARICOSE VEIN DEFINITION	DIAGNOSIS [d]	PREVALENCE (%)	
							MALE	FEMALE
Sisto	1995	Finland	8,000	> 30	Varicose veins diagnosed by a doctor	Questionnaire	6.8	24.6
Canonico	1998	Italy	1,319	> 65	Any reticular or truncal visible varicosity of the lower limb	Examination	17.0	35.2
Evans	1999	Scotland	1,566	18-64	Dilated subcutaneous tortuous trunk veins (C2 CEAP)	Examination	39.7	32.2
Preziosi	1999	France	3,065	35-60	Dilated, tortuous and visible veins of the lower extremities (C2 CEAP_	Examination	10.8	18.1
Criqui	2003	USA	2,211	40-79	Dilated subcutaneous tortuous trunk veins (C2 CEAP)	Examination	15.0	27.7
Jawien	2003	Poland	40,095	16-97	Dilated subcutaneous tortuous trunk veins (C2 CEAP)	Examination	28.0	35.0

[a] First author
[b] Year of publication
[c] Age in years
[d] Method of varicose vein diagnosis

TABLE 2.2 PREVALENCE OF VARICOSE VEINS BY SEX FROM SURVEYS OF THE GENERAL POPULATION (CONTINUED)

AUTHOR [a]	YEAR [b]	LOCATION	SAMPLE SIZE	AGE [c]	VARICOSE VEIN DEFINITION	DIAGNOSIS [d]	PREVALENCE (%)	
							MALE	FEMALE
Rabe	2003	Germany	3,072	18-79	Dilated subcutaneous tortuous trunk vein (C2 CEAP)	Examination	12.4	15.8
Carpentier	2004	France	835	≥ 18	Enlarged, tortuous subcutaneous veins (C2 CEAP)	Examination	30.1	50.5
Chiesa	2005	Italy	5,187	18-90	Dilated subcutaneous tortuous trunk veins (C2 CEAP)	Examination	29.3	29.4

[a] First author
[b] Year of publication
[c] Age in years
[d] Method of varicose vein diagnosis

TABLE 2.3 PREVALENCE OF CHRONIC VENOUS INSUFFICIENCY (CVI) BY SEX IN DIFFERENT STUDIES

AUTHOR [a]	YEAR [b]	LOCATION	STUDY SAMPLE	SAMPLE SIZE	CVI DEFINITION	PREVALENCE (%)	
						MALE	FEMALE
Arnoldi	1958	Denmark	Clinic attendees aged > 25 years	n = 1,981	Active or healed ulcer	1.9	5.5
Bobek	1966	Czechoslovakia	General population aged > 15 years	Males = 6,540	Hyper-depigmented areas	1.9	3.4
				Females = 8,520	Active or healed ulcer	0.9	1.1
Mekky	1969	England and Egypt	Female cotton workers	English = 504 Egyptian = 467	Hyperpigmentation, ulcer, oedema, and eczema	-	10.0
Coon	1973	Tecumseh, USA	General population > 10 years	Males = 3,026	Stasis skin change*	3.0	3.7
				Females = 3,363	Active or healed ulcer	0.1	0.3
Widmer	1978	Basle, Switzerland	Chemical industry employees	Males = 3,744	Skin changes**	6.0	5.0
				Females = 785	Active or healed ulcer	1.0	1.0
Franks	1992	UK	Men and women from general practices	n = 1338	Active or healed ulcer	4.7	4.0

[a] First author
[b] Year of publication
* Excluding varicose veins, ** Hyperpigmentation, fibrosis, induration, atrophy

TABLE 2.3 PREVALENCE OF CHRONIC VENOUS INSUFFICIENCY (CVI) BY SEX IN DIFFERENT STUDIES (CONTINUED)

AUTHOR [a]	YEAR [b]	LOCATION	STUDY SAMPLE	SAMPLE SIZE	CVI DEFINITION	PREVALENCE (%)	
						MALE	FEMALE
Komsuoglo	1994	Turkey	Hospital patients aged > 60 years	n = 850	Hyperpigmentation	0.3	2.8
					Eczema	0.5	1.8
					Active or healed ulcer	0.6	1.4
Ruckley	2002	Edinburgh, UK	General population aged 18-64 years	Males = 699	Hyperpigmentation	1.3	1.1
				Females = 867	Active or healed ulcer	1.0	0.2
Criqui	2003	San Diego, USA	Employees of the University of California	Males = 780	Trophic skin changes***	7.8	5.3
				Females = 1431	Oedema	7.4	4.9
Rabe	2003	Bonn, Germany	General population aged 18-79 years	Males = 1,350	C3 CEAP	11.6	14.9
				Females = 1722	C4 CEAP	3.1	2.7
					C5 CEAP	0.6	0.6
					C6 CEAP	0.1	0.1

[a] First author
[b] Year of publication
*** Trophic skin changes = C4 pigmentation and eczema

TABLE 2.3 PREVALENCE OF CHRONIC VENOUS INSUFFICIENCY (CVI) BY SEX IN DIFFERENT STUDIES (CONTINUED)

AUTHOR [a]	YEAR [b]	LOCATION	STUDY SAMPLE	SAMPLE SIZE	CVI DEFINITION	PREVALENCE (%)	
						MALE	FEMALE
Carpentier	2004	France	Patients of primary care physicians	Males = 277 Females = 132	C3 CEAP	1.1	2.2
					C4 CEAP	4.0	2.1
					C5 CEAP	1.4	0.7
					C6 CEAP	0	0
Chiesa	2005	Italy	Volunteers from general population, aged > 18 years	Males = 730 Females = 4,457	C3 CEAP	11.4	13.9
					C4 CEAP	5.2	3.1
					C5 CEAP	11.6	8.1
Sam	2007	UK	Asian men attending a mosque, mean (IQR) age 67 (62.3-72.8) years	Males = 100	C4 CEAP	6.0	-
					C5/C6 CEAP	0	-

[a] first author
[b] year of publication

TABLE 2.4 SUMMARY OF STUDIES EXAMINING THE ASSOCIATION BETWEEN FAMILY HISTORY AND VARICOSE VEINS

AUTHOR [a]	YEAR [b]	LOCATION	STUDY TYPE	STUDY SAMPLE	FAMILY HISTORY [c]	ASSOCIATION [d]
Mekky	1969	UK	Cross-sectional	504 females aged 15-74 years	Self-reported	p<0.001
Dindelli	1989	Italy	Cross-sectional	611 women aged 15-47 years	Self-reported	OR 5.8 (95% CI 3.8-8.9)
Stvrtinova	1991	Slovakia	Cross-sectional	Store workers aged < 19-60+ years	Self-reported	p<0.01
Sadick	1992	USA	Cross-sectional	Clinic patients aged 18-74 years	Self-reported	p<0.0001
Schultz-Ehrenberg	1992	Germany	Follow -up	Schoolchildren aged 10-12 years	Self-reported	p<0.05 (aged 18-20 y)
Cornu-Thenard	1994	France	Cross-sectional	67 varicose vein cases + 134 parents, 67 controls + 134 parents.	Examination	p<0.001
Komsuoglu	1994	Turkey	Cross-sectional	856 general population aged ≥ 60 years	Self-reported	p=0.001
Scott	1995	USA	Case-control	129 varicose vein cases, 113 controls	Self-reported	OR 21.5 (95% CI 10.0-46.3)
Lee	2003	Edinburgh UK	Cross-sectional	1,566 men and women aged 18-64 years	Self-reported	OR 1.5 (95% CI 1.0-2.3) P* OR 2.2 (95% CI 1.4-3.4) M**

a First author
b Year of publication
c Method of determining family history of venous disease
d Association between family history of venous disease and varicose veins
p = p value < 0.05 denotes statistical significance
OR = odds ratio (95% confidence interval), *Paternal family history, **Maternal family history

TABLE 2.4 SUMMARY OF STUDIES EXAMINING THE ASSOCATION BETWEEN FAMILY HISTORY AND VARICOSE VEINS (CONTINUED)

AUTHOR [a]	YEAR [b]	LOCATION	STUDY TYPE	STUDY SAMPLE	FAMILY HISTORY [c]	ASSOCIATION [d]
Laurrika	2002	Tampere	Cross-sectional	3,284 men and 3,590 women aged 40-60 years	Self-reported	OR 4.9 (95% CI 4.2-5.7)
Carpentier	2004	France	Cross-sectional	8,000 men and women	Self-reported	OR 3.5 (95% CI 1.9-6.5) P* OR 3.5 (95% CI 2.4-5.1) M**
Kroeger	2005	Germany	Cross-sectional	4,250 men and 2,380 women civil employees	Self-reported	OR 3.7 (95% CI 3.0-4.6) P* OR 2.8 (95% CI 2.4-3.3) M**
Criqui	2007	San Diego, USA	Cross-sectional	2,211 university employees aged 40-79 years	Self-reported	OR 2.9 (95% CI 1.8-4.6) P* OR 2.3 (95% CI 1.8-3.1) M**
Pospíšilová	2008	Czech	Clinic-based	319 phlebology patients aged 16-80 years	Self-reported	87% of varicose vein patients FH

[a] First author
[b] Year of publication
[c] Method of determining family history of venous disease
[d] Association between family history of venous disease and varicose veins
p = p value < 0.05 denotes statistical significance
OR = odds ratio (95% confidence interval)
*Paternal family history
**Maternal family history

TABLE 2.5 SUMMARY OF STUDIES EXAMINING THE ASSOCIATION BETWEEN PREGNANCY AND VARICOSE VEINS

AUTHOR [A]	YEAR [B]	LOCATION	STUDY TYPE	STUDY SAMPLE	ASSOCIATION [C]
Mekky	1969	England + Egypt	Cross-sectional	504 women aged 15-74 years	Prevalence higher in 15-34 year olds
Widmer	1978	Switzerland	Cross-sectional	785 female employees	Prevalence higher in multiparous women
Abramson	1981	Israel	Cross-sectional	2,257 women	Age-adjusted OR 0.17 ever pregnant No association with no. of pregnancies
Maffei	1986	Brazil	Cross-sectional	1,312 women aged > 15 years	Prevalence increased with no. of pregnancies
Dindelli	1989	Italy	Hospital-based	611 women aged 15-47 years	OR 2.0 (95% CI 1.3-2.9) ≥ 1 pregnancy
Hirai	1990	Japan	Cross-sectional	541 women aged 15-90 years	Prevalence higher in multiparous women but association only significant in younger women
Stvrtinova	1991	Slovakia	Cross-sectional	696 women	Prevalence increased ≥ 1 pregnancy (p<0.001)
Komsuoglu	1994	Turkey	Cross-sectional	Women aged > 60 years	Prevalence increased ≥ 1 pregnancy
Sisto	1995	Finland	Cross-sectional	3,456 women	OR 1.4 (95% CI 1.0-1.9) 1 pregnancy OR 3.0 (95% CI2.3-4.1) 3 pregnancies

[a] First author
[b] Year of publication
[d] Association between pregnancy and varicose veins
p = p value < 0.05 denotes statistical significance
OR = odds ratio (95% confidence interval)

TABLE 2.5 SUMMARY OF STUDIES EXAMINING THE ASSOCIATION BETWEEN PREGNANCY AND VARICOSE VEINS (CONTINUED)

AUTHOR [A]	YEAR [B]	LOCATION	STUDY TYPE	STUDY SAMPLE	ASSOCIATION [C]
Laurrikka	2002	Finland	Cross-sectional	3,590 women aged 40-60 years	OR 1.8 (95% CI 1.2-2.8) increasing number of births
Criqui	2003	San Diego	Cross-sectional	1,431 women aged 15-70	OR 1.14 (95% 1.03-1.27) ever pregnant
Carpentier	2004	France	Cross-sectional	558 subsample women from 8000 study participants	OR 1.98 (95% CI 1.20-3.25) (p=0.007) ≥ 1 pregnancy
Chiesa	2005	Italy	Cohort	4,457 women	Prevalence 19.6%, 35.0% and 50.0% with 0,3 and 4 pregnancies respectively
Weddell	1969	UK	Cross-sectional	160 women aged ≥ 15 years	No association (p>0.20)
Guberan	1978	Switzerland	Cross-sectional		Prevalence increased with number of children but not significant when adjusted for age
Richardson	1977	New Zealand	Cross-sectional		No association
Scott	1995	USA	Case-control	129 varicose vein cases and 113 controls	No association after adjusting for age
Lee	2003	Edinburgh, UK	Cross-sectional	867 women aged 18-64 years	No association (p>0.05)

[a] First author
[b] Year of publication
[d] Association between pregnancy and varicose veins
p = p value < 0.05 denotes statistical significance
OR = odds ratio (95% confidence interval)

TABLE 2.6 SUMMARY OF STUDIES EXAMINING THE ASSOCIATION BETWEEN VARICOSE VEINS AND MOBILITY AT WORK

AUTHOR [a]	YEAR [b]	LOCATION	STUDY TYPE	STUDY SAMPLE	MOBILITY [c]	ASSOCIATION [d]
Guberan	1992	USA	Clinic-based	1,000 women aged 18-74 years	Standing	Yes
Pinto	1995	Italy	Outpatients	48 men and 152 women, Aged > 15 years	Standing	Yes
Sisto	1995	Finland	Cross-sectional	3,895 women, aged > 30 years	Standing	Yes
Laurikka	2002	Tampere, Finland	Cross-sectional	5,580 men and women aged 40-70 years	Sitting/standing	OR 1.6 (95% CI 1.4-1.8) for standing
Lee	2003	Edinburgh, UK	Cross-sectional	1,566 men and women age 18-64 years	Sitting/standing/walking/heavy lifting	Standing at work in women only (P<0.05)

[a] First author
[b] Year of publication
[c] Measure of mobility at work
[d] Association between mobility at work and varicose veins
p = p value < 0.05 denotes statistical significance
OR = odds ratio (95% confidence interval)

TABLE 2.6 SUMMARY OF STUDIES EXAMINING THE ASSOCIATION BETWEEN MOBILITY AT WORK AND VARICOSE VEINS (CONTINUED)

AUTHOR [a]	YEAR [b]	LOCATION	STUDY TYPE	STUDY SAMPLE	MOBILITY [c]	ASSOCATION [d]
Maffei	1986	Brazil	Clinic-based	1,000 women aged 18-74 years	Sitting/standing/walking	No
Stvrtinova	1991	Slovakia		696 female store workers	Sitting/standing	No
Scott	1995	USA	Case-control	23 men and 106 women Mean (SD) age 43.7 (1.3) years	Standing	No
Canonico	1998	Italy	Cross-sectional	560 men and 759 women Age 66-96 years	Lifetime occupation	No association after adjusting for sex

[a] First author
[b] Year of publication
[c] Measure of mobility at work
[d] Association between mobility at work and varicose veins
p = p value < 0.05 denotes statistical significance
OR = odds ratio (95% confidence interval)

TABLE 2.7 SUMMARY OF STUDIES EXAMINING THE ASSOCIATION BETWEEN OBESITY AND VARICOSE VEINS

AUTHOR [a]	YEAR [b]	LOCATION	STUDY TYPE	STUDY SAMPLE	OBESITY [c]	ASSOCIATION [d]
Abramson	1981	Israel	Cross-sectional	2,245 men and 2,557 women	Weight (kg)	Varicose vein patients mean 3.8 kg heavier after adjusting for age and sex ($p<0.001$)
Canonico	1998	Italy	Cross-sectional	560 men and 759 women aged 66-96 years	BMI<23 kg/m^2 BMI 23-28 kg/m^2 BMI > 28 kg/m^2	$p<0.001$ for BMI>28 kg/m^2 in women. No association in men
Iannuzzi	2002	Italy	Cross-sectional	104 women aged 48-65 years	BMI > 30 kg/m^2	OR 5.8 (95% CI 1.2-28.2) after adjusting for age and sex hormones
Dindelli	1989	Italy	Hospital based	611 women aged 15-47 years	Weight 20% greater than ideal	OR 1.0 (95% CI 0.5-1.8)

[a] First author
[b] Year of publication
[c] Definition of obesity
[d] Association between obesity and varicose veins
BMI = body mass index
p = p value < 0.05 denotes statistical significance
OR = odds ratio (95% confidence interval)

CHAPTER 3: AIMS AND OBJECTIVES

3.1 AIMS OF THE THESIS

This thesis presents some of the results from the Edinburgh Vein Follow Up Study. This thesis focusses on the incidence of C2 varicose veins, C3-C6 chronic venous insufficiency and venous reflux ≥ 0.5 seconds duration at follow up, and risk factors associated with the development of these conditions. The aims of this thesis are as follows:

1. To estimate the prevalence of C1-C6 chronic venous disease at follow up
2. To measure the incidence of C2 varicose veins and C3-C6 CVI at follow up
3. To estimate the prevalence of venous reflux ≥ 0.5 seconds duration at follow up
4. To measure the incidence of venous reflux ≥ 0.5 seconds duration at follow up
5. To examine the relationship between the prevalence of venous reflux ≥ 0.5 seconds duration at baseline and the incidence of C2 varicose veins and C3-C6 CVI at follow up.
6. To determine the association between risk factors at baseline and the incidence of C2 varicose veins and C3-C6 CVI at follow up.
7. To determine the association between risk factors at baseline and the incidence of venous reflux ≥ 0.5 seconds duration at follow up.

3.3 OBJECTIVES OF THE THESIS

The specific objectives to be addressed in this thesis are as follows:

1. To determine the incidence and severity of C2 varicose veins at follow up by:
    - age and sex
    - leg
    - social class

2. To determine the incidence and severity of C3-C6 chronic venous insufficiency at follow up by:
    - age and sex
    - leg
    - social class

3. To determine the prevalence of venous reflux ≥ 0.5 seconds at follow up by:
    - venous system
    - vein segment
    - age and sex

4. To determine the incidence of venous reflux ≥ 0.5 seconds at follow up by:
    - venous system
    - vein segment
    - age and sex

5. To examine the relationship between the presence of reflux ≥ 0.5 seconds at baseline and the incidence of C2 varicose veins at follow up by:
    - venous system
    - vein segment
    - number of vein segments
    - severity of disease

6. To examine the relationship between the presence of reflux ≥ 0.5 seconds at baseline and the incidence of C3-C6 CVI at follow up by:
    - venous system
    - vein segment
    - number of vein segments
    - severity of disease

7. To measure the association of risk factors at baseline with the incidence of C2 varicose veins at follow up, including:
    - body mass index
    - family history of venous disease
    - history of medical conditions associated with chronic venous disease
    - pregnancy, oral contraceptive and hormone replacement therapy use
    - mobility at work
    - smoking
    - bowel habit

8. To measure the association of risk factors at baseline with the incidence of C3-C6 chronic venous insufficiency at follow up, including:
    - body mass index
    - family history of venous disease
    - history of medical conditions associated with chronic venous disease
    - pregnancy, oral contraceptive and hormone replacement therapy use
    - mobility at work
    - smoking
    - bowel habit

9. To measure the association of risk factors at baseline with the incidence of venous reflux ≥ 0.5 seconds at follow up, including:
    - body mass index
    - family history of venous disease
    - history of medical conditions associated with chronic venous disease
    - pregnancy, oral contraceptive and hormone replacement therapy use
    - mobility at work
    - smoking
    - bowel habit

CHAPTER 4: METHODS

4.1 CHAPTER OUTLINE

The Edinburgh Vein Study is the first large population-based study in the UK and one of a few in the world, to investigate chronic venous disease (CVD) using duplex ultrasound to measure venous reflux. The study comprises two stages: baseline and follow up. The baseline study conducted from 1994-1996, measured the prevalence of CVD and established a cohort of participants to study over time. The follow up study conducted from 2007-2009, measured the incidence, progression and risk factors associated with CVD. This thesis is focussed on the follow up study, in particular, the incidence of C2 varicose veins, C3-C6 CVI and venous reflux ≥ 0.5 seconds duration, and risk factors associated with the development of these conditions. The specific aims and objectives of this thesis have already been discussed (Chapter 3).

This chapter will describe the methodology used in the Edinburgh Vein Study. Firstly a summary of the baseline study methods will be provided. The rest of this chapter will focus on the methodology used in the follow up study. The process of tracing and recruiting participants will be outlined. A detailed account of the study measurements, including the clinical examination of the legs and questionnaire, will be given. Lastly, statistical analysis of the study data will be summarised. Quality control measures were undertaken throughout the course of the study but the methods and results will be discussed in Chapter 5.

4.2 BASELINE STUDY

4.2.1 Sample size

The baseline study was a cross-sectional survey of a random sample of the general population of Edinburgh. The sample size at baseline was based on the number of participants required to estimate the prevalence of CVD with precision. The sample size also had to be sufficient enough to enable a subsequent follow up study to be conducted. The prevalence of varicose veins and CVI was assumed to be 20%. Therefore, 1,500 participants were required to give this prevalence a precision of ±2%. If 50% of the 1,500 baseline participants were followed up, assuming a 10% incidence of varicose veins and CVI, an odds ratio of 1.5 or more could be detected. These calculations assumed a 5% significance level with 90% power (Evans 1997).

4.2.2 Sample recruitment

Participants were selected from computerised age-sex registers of twelve general practices, distributed geographically and socioeconomically throughout the city of Edinburgh. They were divided into 10-year age bands for sex, and random sampling was carried out within each age-sex group. Invitation letters were sent to 4,103 prospective participants. Of those, 1,155 had moved away (n=618) or were uncontactable (n=537). Of the 2,948 living in Edinburgh and thus eligible to participate, 998 refused and 348 withdrew, resulting in a study population of 1,566 and a final response rate of 54% (Evans 1997).

4.2.3 Study measurements

The study measurements at baseline comprised an examination of the legs for signs of CVD, duplex ultrasound to measure venous reflux, a questionnaire, measures of height and weight, blood sampling and a 3-day diary of bowel habit. Classification of CVD was based on the Basle system, which was the only available classification system at the time. Photographs of the legs were also taken to document evidence of CVD and allow comparisons between observers. The duplex ultrasound scan measured venous reflux at eight points along the deep and superficial veins in both legs. The self-administered questionnaire enquired about venous history, reproductive history, smoking, dietary fibre and mobility at work. Precise details of the examination procedure at baseline have been published (Evans 1997).

4.3 FOLLOW UP STUDY DESIGN

The follow up study design was a population-based prospective cohort in which the study sample already examined at baseline underwent a 13 year follow up examination. Prospective cohorts are particularly useful in determining the incidence of a disease and associated risk factors. People free of disease are studied longitudinally to observe how many develop the disease (incidence) and exposure to risk factors measured. The study was funded by the Chief Scientist Office, part of the Scottish Government Health and Social Care Directorate and approved by the Lothian Research Ethics Committee.

4.4 FOLLOW UP STUDY POPULATION

The study population comprised the cohort of 1,566 men and women aged 18-64 who took part in the Edinburgh Vein Study. Before the follow up study was undertaken, a preliminary search of the Lothian Community Health Index was conducted to assess how many baseline participants were alive and living in Edinburgh. A search for every 10th participant (n=156) revealed that 85% of the baseline participants would potentially be eligible to participate in the follow up. It was expected that the response to follow up would be higher than the 54% response achieved at baseline, as participants were known volunteers and previous participation should not have been unpleasant or uncomfortable.

4.4.1 Sample recruitment

Prior to recruiting participants for the follow up study, it was necessary to identify those who had died or changed address since taking part at baseline. A list of names, addresses and dates of birth of the 1,566 baseline participants, was sent to the Practitioner Services Division (PSD) of the NHS National Services Scotland (NHS NSS). PSD aids the transfer of medical records between general practitioner (GP) practices to ensure that patient registers are accurate and up to date. Staff at PSD linked each participant's details to the Community Health Index (CHI), a register containing health information of all patients in NHS Scotland, identified by a unique number. This linkage provided up to date information including any deaths, changes to name and address, and current GP. A summary of this process is displayed in Figure 4.1.

Patients who had died since participating at baseline were subsequently removed from the list of those invited to take part in the follow up study. Where a patient no longer resided in Scotland but still lived in the UK, PSD referred to the General Register Office for Scotland (GROS). GROS has an established National Health Services Central Register (NHSCR), which holds patient details such as NHS number, CHI number and health authority based on GP registration. Using the unique CHI number, a search of the NHSCR identified the name of the local health authority in which the patient was registered with a GP. Public health consultants were identified for each health authority, contacted by telephone and notified about the study. Due to data protection, health authorities were not allowed to disclose patient addresses, so an invitation pack was forwarded to the patient by them at our request.

A letter of invitation signed jointly by the research fellow and principal investigator was sent to each baseline participant, inviting them to take part in the follow up study and attend a research clinic for an examination of their legs [Appendix 5]. Travel and accommodation expenses were offered and it was stated that participants' GPs would be notified of the examination results. Enclosed with the invitation letter was a patient information sheet which outlined the purpose of the study, detailed what participation in the study would involve, highlighted data confidentiality and stated where the study results would be published [Appendix 6]. A newsletter summarising the results from baseline [Appendix 7], a reply form [Appendix 8] and a pre-paid envelope were also enclosed in the invitation pack.

A detailed summary of the process of recruiting participants living in Scotland is provided in Figure 4.2. After sending the initial letter of invitation, a period of four weeks was given for the participant to reply. If a reply had been not received within this time period, a second letter of invitation was sent. For those who did not respond to the second invitation, a minimum of three attempts were made to contact them by telephone, where numbers were available. Those who could not be contacted by telephone were deemed "no response". Those whose letters were returned either by the Post Office or a subsequent occupier, were counted as "returns" and a further check was carried out by PSD using the CHI for identification [Figure 4.2].

Upon receiving an affirmative reply, an appointment at a time and date suitable for the participant, was arranged by telephone. A confirmation letter [Appendix 9], map of the research clinic [Appendix 10] and questionnaire [Appendix 11] were sent. One week before, participants were contacted by telephone to remind them of their appointment. Those who did not attend were offered another appointment by telephone. A maximum of three appointments were offered. Those who withdrew from the study or ultimately failed to attend after agreeing to participate were counted as "withdrawals" [Figure 4.2]. Those who refused to participate in the follow up study, or who initially agreed to attend but then subsequently withdrew, were sent a one page questionnaire [Appendix 12]. Questions inquired about previous diagnosis and treatment of varicose veins. They were asked whether they themselves thought they had varicose veins and were given a number of options to state as a reason why they did not want to participate in the follow up study. Analysis of this questionnaire will be presented in Chapter 6.

4.4 FOLLOW UP STUDY MEASUREMENTS

Clinical examinations were held at the Wellcome Trust Clinical Research Facility (WTCRF) at the Western General Hospital, Edinburgh from September 2007 to October 2009. The WTCRF is a clinic dedicated to conducting research and employs nurses with experience of taking repeated, standardised study measurements. Before any measurements were taken, each participant was asked to read a consent form and sign two copies [Appendix 13]. One copy was given to the participant and the other was kept in their file. Participants were also asked to provide details of an emergency contact and notes were made regarding any health conditions and current medication. Data from the examination were documented on specially designed recording forms with the participant's unique study reference number and the initials of the research staff member conducting the appointment [Appendix 14].

Participants were examined by one member of the research team, which comprised two WTCRF research nurses, the research fellow (and author of this thesis) and the study assistant. All four were specially trained in the methods of classification of CVD and duplex ultrasound scanning to assess venous reflux in the legs (Training in classification of CVD and duplex ultrasound will be discussed in sections 4.4.3 and 4.4.4 respectively). The study examination included a measure of height and weight, questionnaire, leg examination and photographs, and duplex ultrasound of the leg veins to measure venous reflux. Each examination took approximately one hour.

4.4.1 Height and weight

Participants' height was measured once to the nearest 5mm, without shoes, using a free standing stadiometer. Weight, without shoes or outdoor clothes, was measured to the nearest 100g on a digital scale. The stadiometer and scales were periodically calibrated against another instrument. Body mass index (BMI) was calculated using the following equation:

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

Participants with a BMI of < 18.5 kg/m^2 were classified us "underweight", 18.5-24.99 kg/m^2 as "normal weight", 25 to <30 kg/m^2 as "overweight" and ≥ 30 kg/m^2 as "obese", in accordance with the World Health Organization's criteria (WHO 2000).

4.4.2 Questionnaire

A self-administered questionnaire was completed by all participants prior to their examination and checked by the research staff at the appointment [Appendix 11]. The questionnaire was amended from that at baseline to identify changes in exercise and other lifestyle factors during the follow up years. In addition, questions from the VEINES-QOL/Sym (Lamping 2003) were also included. The VEINES-QOL/Sym has been discussed in Chapter 1, Section 1.6.2. It is modelled on the SF-36 but is specific to CVD. Responders are asked about symptoms, daily limitations, and psychological impact of CVD within the past 4 weeks, rated on a 2-point to 7-point scale of intensity, frequency, or agreement.

Topics covered in the study questionnaire include the participant's general health, leg problems and symptoms, past relevant medical history including details of treatment for varicose veins and venous ulcers, family history of CVD, smoking history and physical exercise. Mobility at work, measured by the proportion of time spent sitting, standing, walking or heavy lifting, was also documented. An obstetric history and use of oral contraceptives and hormone replacement therapy was obtained for all female participants. In addition, the research staff recorded participant's ethnic origin as one of the following: White Caucasian, African, Indian, Chinese or other (to be specified).

4.4.3 Classification of chronic venous disease

The classification system used in the follow-up study was slightly different to that adopted at baseline. At baseline, the classification of CVD was based on the Basle System, with telangiectases, reticular veins, varicose veins and CVI split into 3 grades according to severity [Appendix 1]. However, the CEAP classification has since become universally accepted as the most appropriate for venous research and clinical practice [Appendix 2]. In order to permit comparison with the baseline study and ensure comparison with other studies using CEAP, both the Basle and CEAP classifications for CVD were used in the follow up study. For CEAP classes C1 (telangiectases and reticular veins) and C2 (varicose veins), varices were divided into grades 1-3 for severity, according to the Basle classification. Classification of CVI was based on the CEAP classification alone with C3 (corona phlebectatica or oedema), C4 (skin changes such as C4a pigmentation, C4a eczema, C4b lipodermatosclerosis and C4b atrophie blanche), and C5 and C6 (healed and active ulceration respectively) representing increasing severity.

The four members of the research team were trained in the Basle and CEAP classification systems. The original slides from both the Basle and baseline EVS studies were used to provide examples of grades of severity of CVD based on the Basle classification system. Additionally, images showing the CEAP C1-C6 classes of CVD were analysed and definitions of each class studied. Periodically during the study, the research staff re-examined photographic evidence of the Basle and CEAP classifications, to remind them of the original standard of classification and to try to increase observer reliability. Several quality control measures were adopted during the study to increase observer reliability in the classification of CVD. These measures and results will be discussed in detail in Chapter 5.

Leg examination

All participants had their legs examined for signs of CVD using the Basle and CEAP classifications discussed above. Participants stood on a raised platform with their feet in three standard positions: facing towards the observer with heels together and forefeet spread apart [Figure 4.3], facing away from the observer with heels together and forefeet spread apart [Figure 4.4] and facing away from the observer with feet parallel [Figure 4.5]. A mat with pre-designated foot positions was used to ensure consistency. Participants were asked to stand for a minimum of two minutes in order to allow the blood to pool in their legs prior to classification. Any scars and notable findings on the legs were documented in the notes section of the recording forms.

Photographs of the legs

Participants had their legs photographed in the Medical Photography studio at the Western General Hospital. Three photographs were taken while the participant stood on the raised platform in the three examination positions described previously [Figures 4.3-4.5]. The camera was positioned at a distance so that the photograph allowed visualisation of the leg from the foot to the groin. Camera and light adjustments were made by the medical photographer, according to skin colour of the participant. For identification purposes, each participant was photographed beside their unique five digit study number. The photographs were saved as a digital image on compact discs in subfolders arranged by the participant's study number.

The digital photographs were subsequently analysed by two members of the study team who had not examined the participant in the clinic. They independently graded the photos according to the Basle/CEAP classification system described above. If the classifications of the two observers viewing the photographs differed, discussion between these observers achieved a consensus classification for each participant. If a consensus could not be reached, the photographs were reviewed by a vascular surgeon who made the final classification. The process of classifying CVD upon examination and subsequent analysis of photographs resulted in two independent classifications of CVD by two observers for each participant.

4.4.4 Duplex ultrasound for venous reflux

The research team underwent extensive training in duplex ultrasound scanning of the leg veins. Training was conducted by a consultant radiologist and two vascular scientists. A range of volunteers were recruited so that the staff could practise scanning leg veins. Staff sat a practical test where they conducted a complete scan of the veins segments, assessed by a vascular scientist. Only when all four researchers were deemed competent in duplex ultrasound, did the study examinations begin. A specific scanning protocol was devised to ensure that the scans were performed in the same way for each participant [Appendix 15].

The duplex ultrasound scans were performed with a real-time, pulsed, Doppler colour flow imaging Philips ATL HDI 5000 Sono CT duplex scanner (Mount International Ultrasound Services Ltd, Gloucester, England). An L7-4 broadband linear array probe with an operating frequency range of 4-7MHz was used. Reflux was induced using a cuff placed around the calf, which was rapidly inflated and deflated using a Hokansen E20 cuff inflator and an AG-101 air source (P.M.S Instruments Ltd, Berkshire, UK). There were two cuff sizes depending on the diameter of the calves (cuff width 10cm, length 50cm or 65cm). A pressure of approximately 110mmHg was used to rapidly inflate the cuff. A minimum time of 5 seconds was given between compressions to ensure that the legs refilled with blood. For vein segments where the compression did not produce sufficient forward flow to measure reflux, a manual squeeze of the calf was employed. For vein segments below the calf (GSV lower calf) a foot squeeze was performed to elicit venous flow.

Before the scan commenced, all participants were asked about their history of varicose vein operations, experience of recurrent fainting or blackouts, and current use of hypotensive drugs. Each participant was examined on a tilting couch (Mount International Ultrasound Services Ltd, Gloucester, England) at an angle of 45°. This position was chosen to provide support to participants and thus prevent fainting during the procedure, while allowing gravity to act on blood within the leg. Where participants felt faint at an angle of 45°, the tilt table was reduced to an angle of 30°. For scanning veins in the thigh and the calf, participants stood with their back to the tilting table and were encouraged to take most of their weight onto the opposite leg and relax the leg to be scanned out to the side, with the knee slightly bent. For scanning veins behind the knee, the participant stood facing the scanner with their side against the tilting table, the leg to be scanned slightly bent at the knee and the weight mainly on the opposite leg (Evans 1997).

The following ten segments of the deep and superficial system were assessed for venous reflux:

Deep veins:

1. Common femoral vein (CFV) proximal to the sapheno-femoral junction (SFJ).
2. Femoral vein (FV) approximately 2cm distal to the confluence with the profunda femoris vein
3. FV in the lower third of the thigh.
4. Popliteal (POP) vein above the knee crease.
5. POP vein below the knee crease.

Superficial veins:

6. Great saphenous vein (GSV) distal to the SFJ
7. GSV in the lower third of the thigh.
8. GSV in the upper calf.
9. GSV in the lower calf.
10. Small saphenous vein (SSV) distal to the sapheno-popliteal junction (SPJ).

When venous flow was induced in the leg being scanned, reflux was identified on the Doppler spectrum [Figure 4.6]. Two spectra were selected at each vein segment and the duration of reflux was measured by placing the cursors at the beginning and end of the period of reflux (Evans 1997). Reflux time was calculated to the nearest hundredth of a second. The mean of the two reflux times at each vein segment was used in all analysis.

In cases where the participant had an unusual venous anatomy and the observer wanted a second opinion, the participant was invited to return for a second scan performed by a vascular scientist, using the same duplex ultrasound machine. If the scan results differed considerably, the reflux measurements of the second scan were used in the analysis. Periodically during the course of the study, duplex scans were performed by two observers on the same participant, or by one observer on the same participant, to allow inter- and intra-observer comparison of results and identification of any problems. The methods and results of these observer variability checks will be reported in Chapter 5.

4.5 DATA ENTRY

Data from recording forms and questionnaires were entered into a specifically designed Microsoft Access database by the research fellow. The database was password protected and data was only identifiable by the participant's unique study number. All data was entered onto a second identical database by the study assistant. Comparison of the two databases revealed any discrepancies which were subsequently checked and corrected. Once the data had been checked, a report summarising the examination results was generated and sent to each participant's GP [Appendix 16].

4.6 STATISTICAL ANALYSIS

Data files were transferred to the Edinburgh University computing network for analysis using the SPSS-X software (SPSS INC., Chicago III). Univariate statistical analysis was conducted to test the association between incidence and risk factors. The chi squared (χ^2) test was used for nominal categorical data, the χ^2 test for linear trend was used for ordered categorical data and the Student's t-test was used for continuous data. A P value of <0.05 was used to denote statistical significance throughout. Unadjusted and adjusted odds ratios with 95% confidence intervals were calculated for the incidence. Risk factors that were statistically significant on univariate analysis were entered into a stepwise logistic regression model adjusted for age and sex, to determine which factors were independently associated with the incidence of C2 varicose veins, C3-C6 CVI and venous reflux ≥ 0.5 seconds duration at follow up.

Data from the clinical examination at baseline and at follow-up were compared to measure the:

- Prevalence of CVD in the follow up sample (C1-C6 CVD)
- Incidence of C2 varicose veins and C3-C6 CVI in the follow up sample
- Prevalence of venous reflux ≥ 0.5 seconds duration in the follow up sample
- Incidence of venous reflux ≥ 0.5 seconds duration in the follow up sample
- Association between venous reflux ≥ 0.5 seconds duration at baseline and incidence of C2 varicose veins and C3-C6 CVI at follow up
- Association between risk factors at baseline and incidence of C2 varicose veins and C3-C6 CVI at follow up
- Association between risk factors at baseline and incidence of venous reflux ≥ 0.5 seconds duration at follow up

Incidence refers to the number of new cases of disease in a population. The incidence of C2 varicose veins is calculated by dividing the number of participants who developed C2 varicose veins at follow up by the number of participants free of C2 varices at baseline. Similarly, incidence of C3-C6 CVI is based on the number of participants with C3-C6 CVI at follow up divided by the number of participants free from C2 varicose veins and C3-C6 CVI at baseline. This thesis does not deal with progression of venous disease. Therefore any participant with C2 varicose veins at baseline who had C3-C6 CVI at follow up would not be included as an incident case as this is not an occurrence of new venous disease but rather progression of existing venous disease. Incidence of venous reflux is measured by dividing the number of participants who developed reflux ≥ 0.5 seconds duration in any vein segment at follow up by the number of participants with no reflux in any vein segment at baseline.

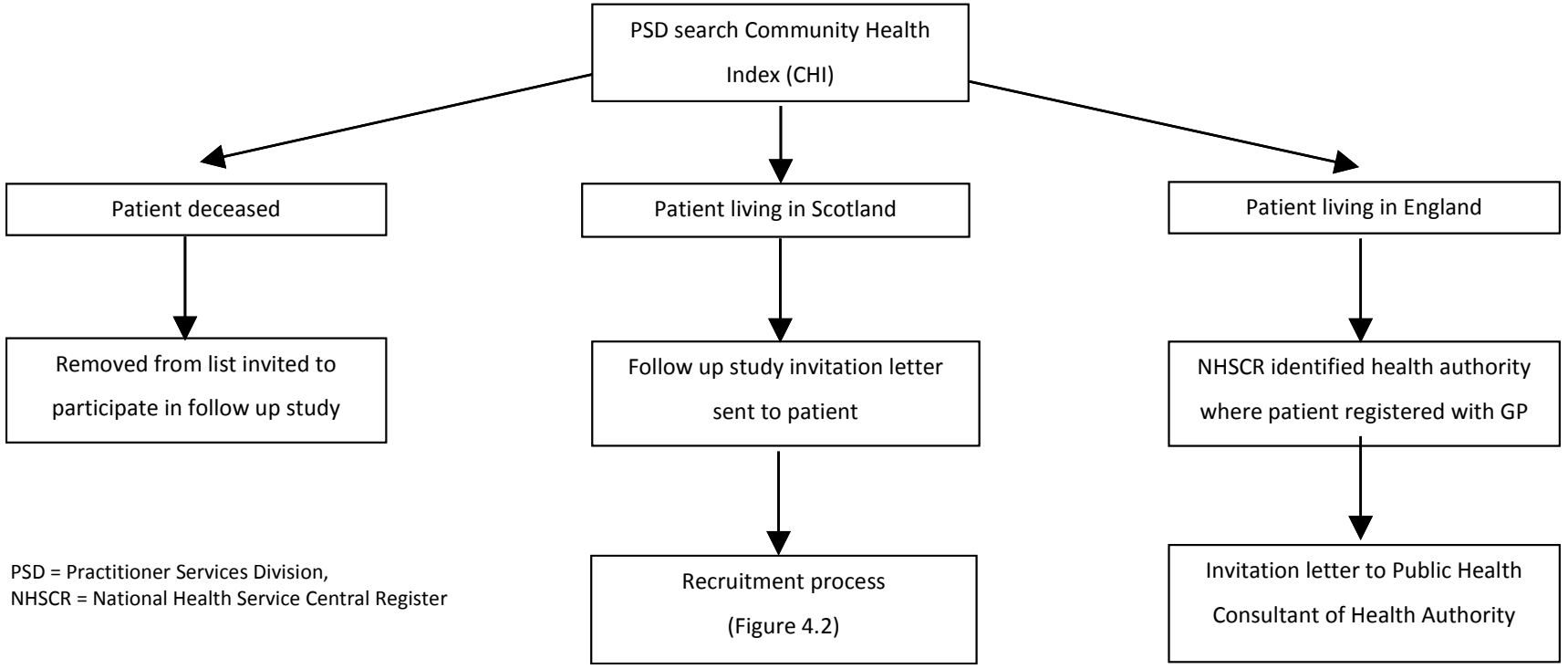
Participants free of C2 varices, C3-C6 CVI or venous reflux at baseline may have developed either of these conditions and had subsequent treatment during the 13 year follow up period. Consequently any symptoms and signs of C2-C6 disease or venous reflux may not have been evident at the follow up examination. The questionnaire administered at follow up enquired about varicose vein treatment including surgery, sclerotherapy and the year that the procedure was carried out. In order to measure the true incidence, any participant free from disease at baseline who had subsequent treatment during the follow up but had no symptoms of C2 varicose veins or C3-C6 CVI at the follow up examination, was included as an incident case.

4.7 CHAPTER SUMMARY

The Edinburgh Vein Follow Up Study was a population cohort study in which survivors of 1,566 individuals aged 18 to 64 years from the general population examined at baseline, were invited to have a 13 year follow up examination. Participants were identified through NHS services and strenuous efforts were undertaken to recruit as many participants as possible. Study examinations were held at a research clinic by one of four trained staff members. The examination comprised a clinical classification of the legs to check for signs of CVD and photographs to document the evidence. A duplex ultrasound scan was conducted at ten vein segments in the deep and superficial systems in both legs to detect the presence of venous reflux. Participants completed a standardised questionnaire which gathered information on past medical history, family history and previous treatment of CVD, smoking status, physical activity and mobility at work. An obstetric history was documented for all female participants. Symptoms of CVD and quality of life were also measured using the VEINES-QOL/Sym questionnaire.

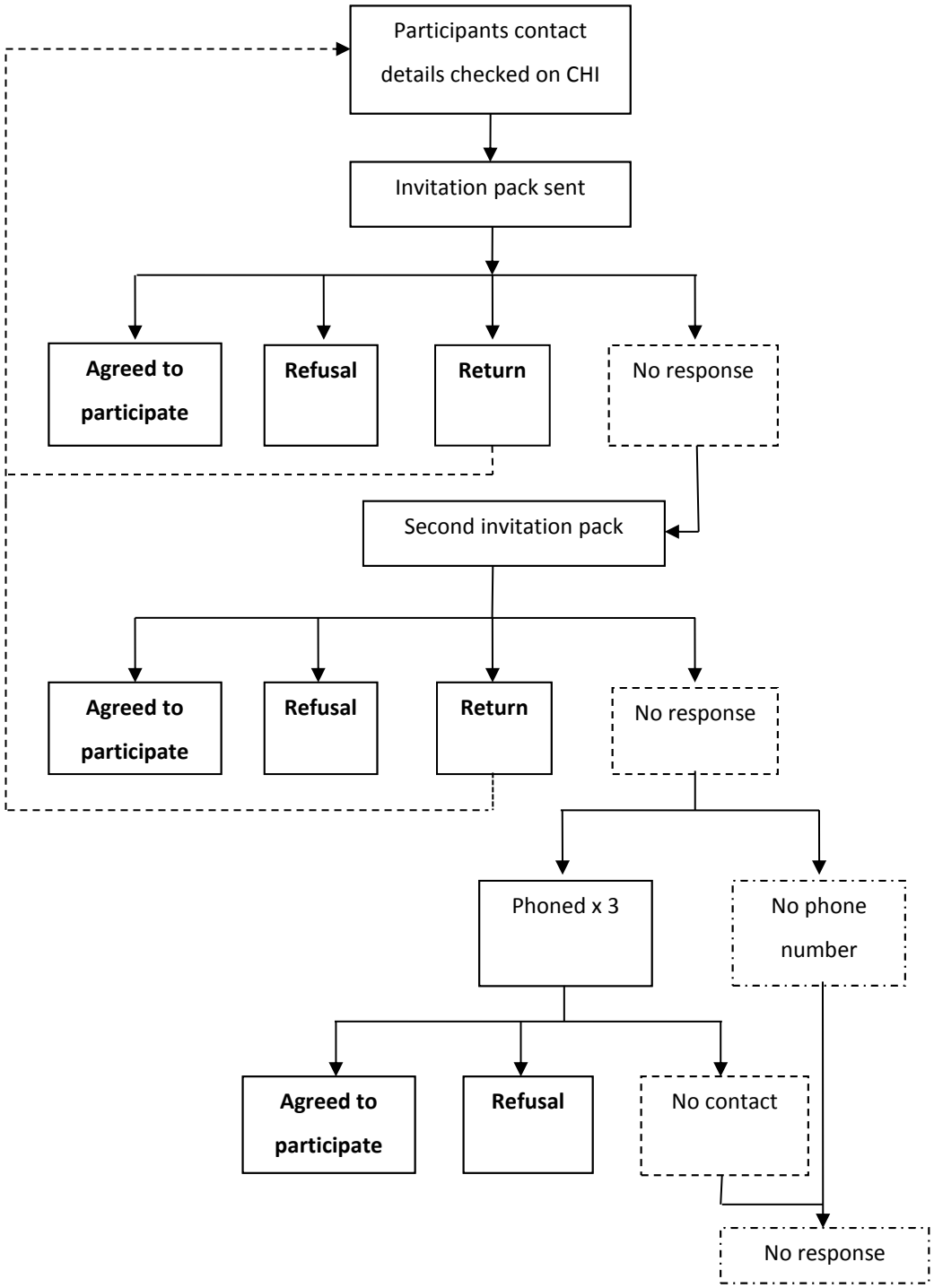
Statistical analysis of the data was performed to measure the incidence of C2-C6 CVD and venous reflux at follow up and risk factors associated with the development of these conditions. Several quality control measures were employed during the study and they will be discussed in the next chapter.

FIGURE 4.1 SUMMARY OF THE PROCESS OF RETRIEVAL OF PATIENT DETAILS FOR INVITATION TO THE FOLLOW UP STUDY



PSD = Practitioner Services Division,
NHSCR = National Health Service Central Register

FIGURE 4.2 RECRUITMENT CYCLE FOR THE EDINBURGH VEIN FOLLOW UP STUDY



"Returns" = baseline participants whose letters were returned by post office or subsequent occupier.
"Unable to trace" = baseline participants with whom no contact was made, despite two invitations and three telephone calls.

FIGURE 4.3 EXAMINATION POSITION 1

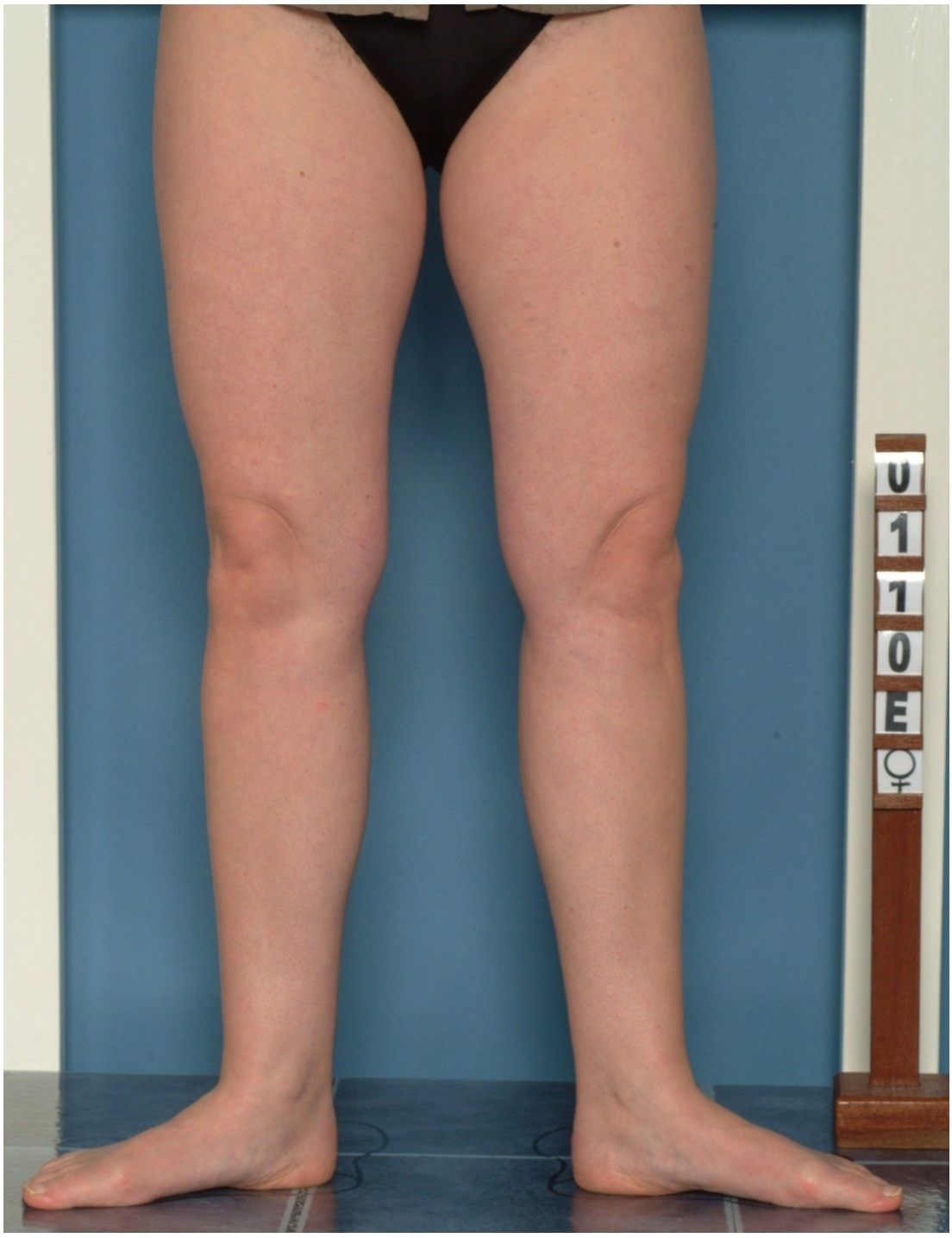


FIGURE 4.4 EXAMINATION POSITION 2

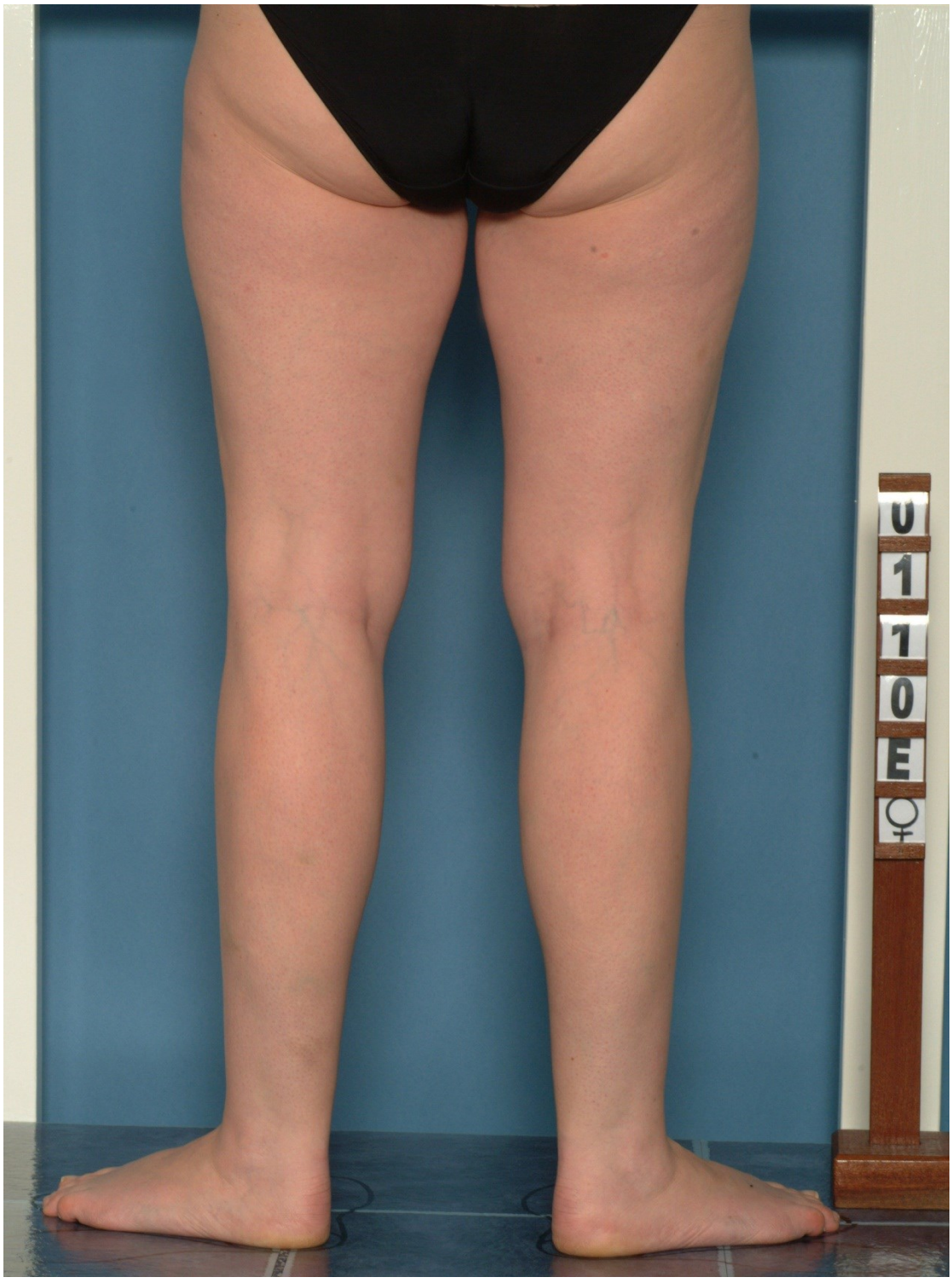


FIGURE 4.5 EXAMINATION POSITION 3

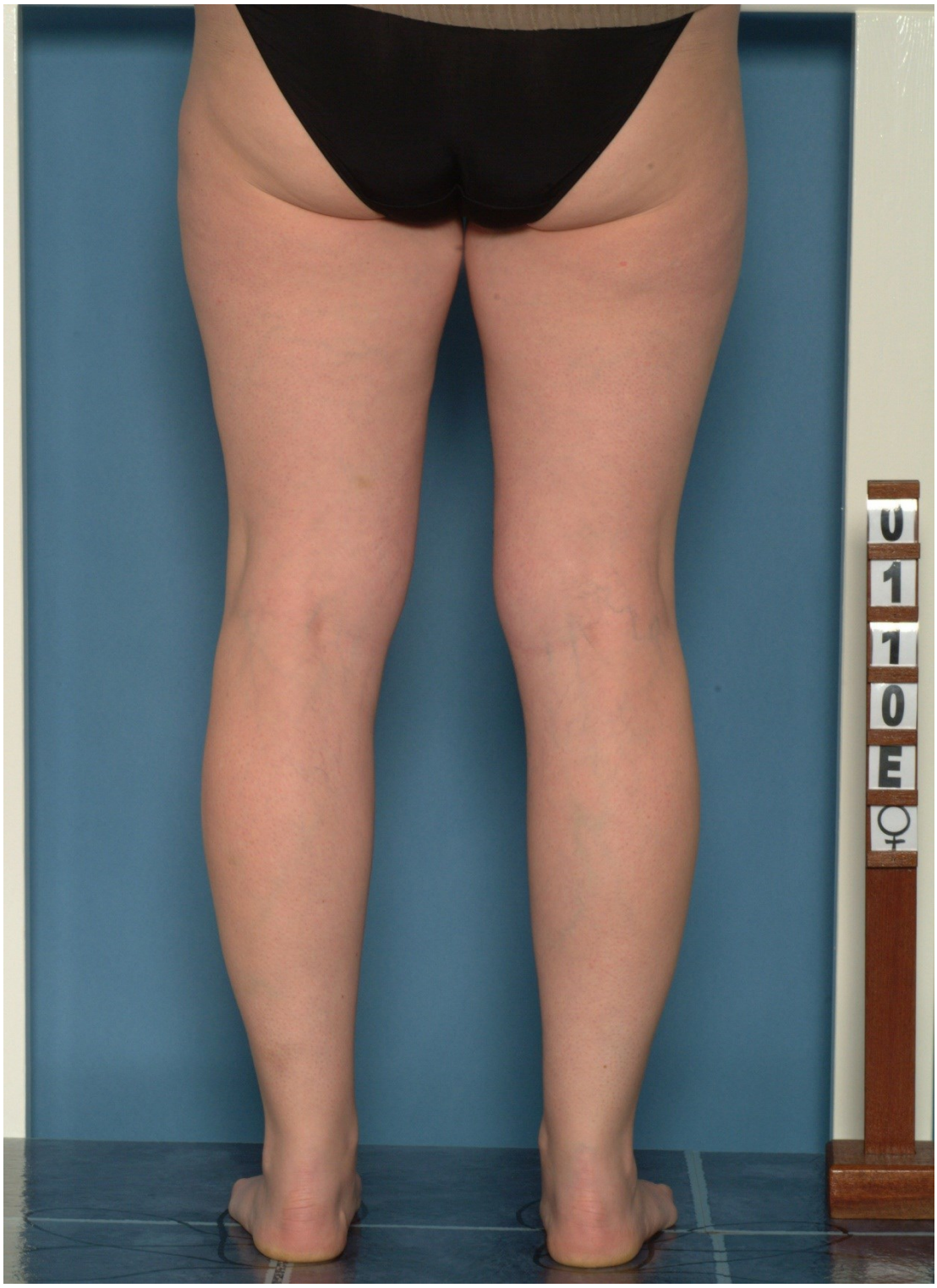
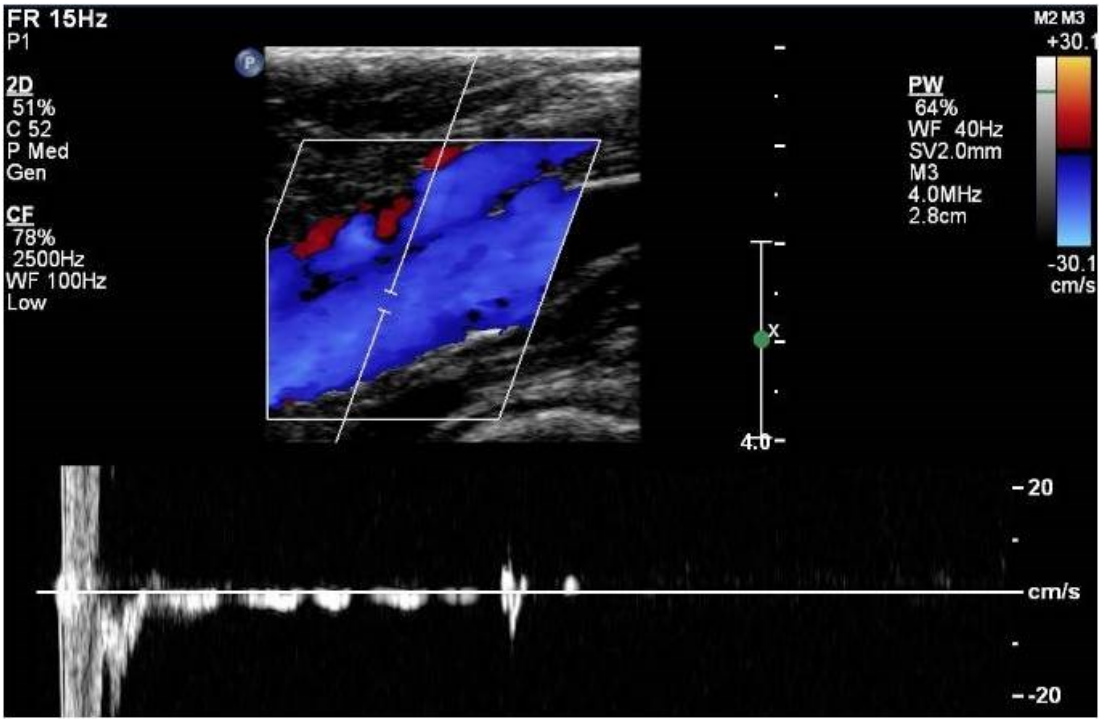


FIGURE 4.6 DUPLEX ULTRASOUND IMAGE IN MEASURING VENOUS REFLUX



CHAPTER 5: QUALITY CONTROL

5.1 CHAPTER OUTLINE

Research studies reporting physical examination findings or results of diagnostic tests, often rely on some degree of subjective interpretation by observers. The Edinburgh Vein Follow up Study employed four different research staff who conducted complex duplex ultrasound examinations to assess venous reflux and followed a strict classification system to diagnose CVD. It was therefore imperative that the reliability of the observers was assessed to ensure that the study data were as accurate as possible. This chapter summarises the methods used to assess observer reliability during the follow up study and presents results of these checks. Four aspects of the classification of CVD were assessed: 1) comparison of classification between baseline and follow up observers, 2) inter-observer reliability at follow up, 3) intra-observer reliability at follow up and 4) comparison of classification based on examination versus photographic evidence at follow up. Two assessments were made regarding venous reflux measurements: inter- and intra-observer reliability at follow up. For reporting comparisons between observers or methods, results are presented as level of agreement (%) with a kappa statistic (K) where possible. A detailed description of the statistical methods used to measure observer variability is provided in Appendix 17.

5.2 CLASSIFICATION OF CHRONIC VENOUS DISEASE

5.2.1 Comparison of baseline and follow up observers

In order to compare the inter-observer variability between observers at baseline and observers at follow up, a sub-sample of 100 baseline participants was created by selecting every 15th from the 1,566 baseline participants. Baseline photographs of the sub-sample were independently classified by two observers participating in the follow up examination. The observers at follow up were unaware of the CVD classification made by the observers at baseline. If the classification of the two observers viewing the photographs differed, discussion between two observers was held until a consensus classification for each participant was achieved. The overall consensus classifications for the follow up observers were compared to the classifications made at baseline to check for any differences in observer variability between the observers at baseline and follow-up. Table 5.1 displays the results.

There was good agreement between the observers at baseline and follow up for C1 telangiectases (88%) and reticular veins (92%). For C2 varicose veins, the level of agreement was 96% (K=0.90). For C3-C6 CVI, the level of agreement for corona phlebectatica was 99% (K=0.88) while for oedema and pigmentation there was 100% agreement (K=1.00) for both conditions. These results suggest that, while some observer variability would be expected between the observers at baseline and follow up, the differences were tolerable, thus permitting a comparison to be made of findings at baseline and follow up.

5.2.2 Inter-observer reliability at follow up

In order to assess reliability between observers at follow up, a random sample of 49 follow up participants were invited for a second clinical examination, a minimum of 12 weeks after their first follow up examination. Due to time constraints at the research facility, only observers 3 and 4 classified the legs. The two observers classified the legs independently of each other. Classification data for both observers were entered into a quality control database, double checked, and statistical analysis was conducted to assess the level of agreement and kappa statistic. Results of this analysis are presented in Table 5.2.

There was good inter-observer agreement (80.8%) for C1 telangiectases (K=0.69). For C1 reticular veins, the kappa value of 0.58 suggested a moderate level of reliability but the level of agreement between observers was 82.6%. For C2 varicose veins, the kappa value could not be calculated as one observer awarded a grade 3 varicose vein while the highest grade awarded by the other observer was a grade 2 varicose vein. Nevertheless the level of agreement between the two observers was almost 77%. For C3-C6 CVI, the inter-observer reliability was high with kappa values ranging from 0.78-1.00 and level of agreement between the two observers ranging from 96-100%.

5.2.3 Intra-observer reliability at follow up

For the assessment of intra-observer reliability, a random sample of 35 follow up participants underwent a second clinical examination and had their legs classified by the same observer who conducted the first examination. This was performed for observers 3 and 4 only. Venous disease classification for examinations 1 and 2 were compared in order to measure the level of agreement for each observer. Results of the intra-observer reliability are presented in Table 5.3.

Observer 3 re-examined 21 participants and there was a good agreement between classifications at examinations 1 and 2, with kappa values between 0.64-1.00 and level of agreement ranging between 76-100%. Within the random sample of 21 participants, there were no cases of C3-C6 CVI except for C4a venous eczema. Observer 4 examined 14 participants. For C1-C2 conditions, kappa values between 0.48 and 0.64 indicated moderate to good reliability and levels of agreement ranged from 71-78%. For C3-C4 CVI including corona, oedema, pigmentation and eczema, the level of agreement was higher, ranging from 85-100%. There was no evidence of C4b lipodermatosclerosis, C4b atrophie blanche or C5 or C6 ulceration within the sample of participants examined by observer 4.

5.2.4 Prevalence of venous disease by observers at follow up

A comparison of the clinical classifications for all participants was made to check for differences in prevalence rates between the four observers. Given that 880 participants were examined at follow up, the prevalence of the C1-C6 classes of CVD would be expected to be similar between observers. This analysis highlighted two suspected observer errors. Observer 3 reported fewer mild (grade 1) C2 varicose veins on examination of the participants (prevalence 15.3% versus mean prevalence of 19.5% for other 3 observers). However, when her classification based on photographic evidence was compared to the other three observers, no difference in the prevalence of grade I varicose veins was found (prevalence 22.6% versus mean prevalence of 21.8% for other 3 observers*)*, suggesting an under reporting on examination only.

The second observer error was that when observer 2 examined the subject in the clinic, she reported a higher prevalence of C4a eczema compared to the other three observers (prevalence 7.8% versus mean prevalence of 2.4% for other 3 observers). Discussion with this observer and examination of her written records indicated that she had different clinical criteria for assigning eczema to a participant. She classified any dry skin on the leg as C4a venous eczema. However, the CEAP definition is "erythematous dermatitis most often located near varicose veins" (Eklöf 2004). The fact that this observer did not look for redness, inflammation and eczema near the varicose vein suggests a misdiagnosis of this condition.

5.2.5 Examination versus photographic classification at follow up

Classifications of CVD on examination were compared to classifications based on analysis of the photographs. Measures of agreement for the two methods were obtained for individual participants, taking the leg with the higher CEAP class or grade of severity as the participant's disease status. Results of the reliability checks are presented in Table 5.4. C1 telangiectases and reticular veins and C3 corona phlebectatica were more likely to be classified at a higher grade from the photographic evidence, while C2 varicose veins were more likely to be classified at a higher grade by the examination method.

5.2.6 Changes made to the data set

Although the preference was to use examination rather than photographic data because the former was more complete (880 participants were examined but only 676 had their legs photographed), the results of the variability checks indicated that the following amendments would improve the accuracy of the data to be included in the statistical analysis:

1. Classification of C1 telangiectases and reticular veins were based on photographic evidence, where available, as this was considered to be the most accurate because the classification was based on consensus between two observers who classified CVD independently of each other

2. Classification of C2 varicose veins was based predominantly on the examination classification. For participants examined by observer 3 who underreported on examination, a grade 0 at clinical examination was corrected to a grade 1 (mild), if that was the finding on photographic evidence. Of 490 participants examined by observer 3, 51 (10.4%) participants had varicose veins corrected from absent to mild, based on the photographic evidence. As a result of these adjustments, the prevalence of mild C2 varicose veins for observer increased from 15.3% (uncorrected) to 25.7% (corrected for known underreporting).

3. Classification of C3-C6 CVI was based predominantly on examination classification with the following adjustments for photographic findings for C3 corona phlebectatica and C4a eczema. C3 corona was seen more frequently in photographs than it was at examination and, as the photographs were independently classified by two observers, it was considered that the data from the photographs was more accurate. C4a venous eczema was based on photographic evidence for observer 2 as it was known that she had over-reported this condition on examination. Initially, observer 2 had classified 25 (7.8%) participants out of 180 examined as having C4a venous eczema. However after reviewing photographic evidence, it was confirmed that only 16 participants had this condition and therefore 9 (5%) participants had venous eczema changed from present to absent.

5.3 VENOUS REFLUX MEASUREMENTS AT FOLLOW UP

To assess observer reliability of reflux measurements, 49 participants underwent a second ultrasound scan. For inter-observer reliability the participant had the same leg scanned by two different observers. The observers performed the scan independently and were unaware of the results obtained by the other observer. For intra-observer reliability, the participant had one leg scanned by the same observer who conducted the first scan, with a minimum of 12 weeks between the scans. All reflux data were entered into a database and double checked. Statistical analysis was performed to measure level of agreement and kappa values for inter- and intra-observer reliability.

5.3.1 Inter-observer reliability at follow up

For inter-observer reliability, observers were grouped into pairs for logistical purposes and to simplify the comparisons to be made. Observers 1 and 2 were paired together and in total they examined 19 participants. Observers 3 and 4 examined 30 participants. Results of the inter-observer reliability analysis are shown in Table 5.5. For deep vein segments such as the CFV and the FV, the prevalence of reflux was very low and the kappa statistic could not be calculated. However, overall the level of agreement for all observers was 98% for these vein segments. Venous reflux in the POP vein was more common. Kappa values of approximately 0.5 indicated moderate reliability but levels of agreement ranging from 83-94% suggested that the inter-observer reliability was higher than the kappa value would suggest. For the superficial vein segments, kappa values for all four observers were all greater than 0.5 indicating moderate agreement. With levels of agreement between 79-95%, the inter-observer reliability for all four observers was acceptable. There were no differences in kappa values or levels of agreement between the two paired groups of observers.

5.3.2 Intra-observer reliability at follow up

Table 5.6 displays the results of intra-observer reliability checks for reflux measurements at follow up. Although the kappa scores for observers 1 and 4 were lower, the levels of agreement for both observers were all greater than 70% indicating good intra-observer reliability. All four observers reported similar levels of agreement ranging from 70-100%, which suggests that each observer achieved similar reflux results at two different examinations.

5.4 CHAPTER SUMMARY

This chapter has discussed the various quality control checks which were applied during the course of this follow up study. Such measures were put in place to ensure that the data obtained was as valid, reliable and generalisable as possible. Analysis showed that overall, the inter- and intra-observer reliability for classification of CVD and measurement of venous reflux were high. Despite these results, the quality control checks did highlight a few minor errors. Consequently appropriate changes were made to the data set in order to improve the accuracy of the data.

TABLE 5.1 COMPARISON OF CHRONIC VENOUS DISEASE CLASSIFICATION BETWEEN OBSERVERS AT BASELINE AND FOLLOW UP, ON A SAMPLE OF 100 BASELINE PARTICIPANTS

CEAP [a]	BASELINE [b] (N)	FOLLOW UP [c] (N)	AGREEMENT [d] (%)	KAPPA [e]
C1 TELANGIECTASIA	100	88	88.0	0.64
Absent	14	12	85.7	
Grade 1	82	74	90.2	
Grade 2	4	2	50.0	
Grade 3	0	0	100.0	
C1 RETICULAR VEINS	100	92	92.0	0.63
Absent	3	2	66.7	
Grade 1	87	84	96.4	
Grade 2	10	6	60.0	
Grade 3	0	0	100.0	
C2 VARICOSE VEINS	100	96	96.0	0.90
Absent	75	74	98.7	
Grade 1	20	18	90.0	
Grade 2	5	4	80.0	
Grade 3	0	0	100.0	
C3 OEDEMA	100	100	100.0	1.00
No	99	99	100.0	
Yes	1	1	100.0	
C4a PIGMENTATION	100	100	100.0	1.00
No	99	99	100.0	
Yes	1	1	100.0	

[a] CEAP = CEAP classification of chronic venous disease (Eklof 2004)
N = number of participants assigned C class of disease by observers at baseline and follow up
[b] Observers at the baseline stage of the Edinburgh Vein Study
[c] Observers at the follow up stage of the Edinburgh Vein Study
[d] Agreement = proportion of participants identified at the same grade of clinical disease by observers at baseline and follow up
[e] Kappa statistic: <0.20=poor, 0.21-0.40=fair, 0.41-0.60=moderate, 0.61-0.80=good, 0.81-1.00=very good

TABLE 5.2 INTER-OBSERVER RELIABILITY FOR CEAP CLASSIFICATION OF CHRONIC VENOUS DISEASE AT FOLLOW UP

	OBSERVERS 3 AND 4	
CEAP [a]	**AGREEMENT (%) [b]**	**KAPPA [c]**
C1 TELANGIECTASES	**80.8**	**0.69**
C1 RETICULAR VEINS	**82.6**	**0.58**
C2 VARICOSE VEINS	**76.9**	**-**
C3 CORONA PHLEBECTATICA	**100.0**	**+**
C3 OEDEMA	**100.0**	**1.00**
C4a PIGMENTATION	**100.0**	**+**
C4a ECZEMA	**96.1**	**0.78**
C4b LIPODERMATOSCLEROSIS	**100.0**	**+**
C4b ATROPHIE BLANCHE	**100.0**	**+**
C5 HEALED ULCER	**100.0**	**+**
C6 ACTIVE ULCER	**100.0**	**+**

[a] CEAP = CEAP classification of chronic venous disease (Eklof 2004)
Based on 49 participants randomly selected for a second examination
[b] Agreement = proportion of participants identified at the same CEAP class between two observers.
[c] Kappa statistic: <0.20 = poor, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = good, 0.81-1.00 = very good
- Kappa statistic could not be calculated as cross tabulation of CEAP condition by the two observers was asymmetrical
+ Kappa statistic could not be calculated as there was no evidence of CEAP condition by observer 3 or 4

TABLE 5.3 INTRA-OBSERVER RELIABILITY FOR CEAP CLASSIFICATION OF CHRONIC VENOUS DISEASE AT FOLLOW UP

	OBSERVER 3 (n=21)		OBSERVER 4 (n=14)	
CEAP [a]	**AGREEMENT (%) [b]**	**KAPPA [c]**	**AGREEMENT (%) [b]**	**KAPPA [c]**
C1 TELANGIECTASES	76.2	0.64	71.4	0.48
C1 RETICULAR VEINS	85.7	-	78.6	0.64
C2 VARICOSE VEINS	90.5	0.84	78.6	0.63
C3 CORONA PHLEBECTATICA	100.0	+	92.9	-
C3 OEDEMA	100.0	+	100.0	1.00
C4a PIGMENTATION	100.0	+	92.9	-
C4a ECZEMA	100.0	1.00	85.7	-
C4b LIPODERMATOSCLEROSIS	100.0	+	100.0	+
C4b ATROPHIE BLANCHE	100.0	+	100.0	+
C5 HEALED ULCER	100.0	+	100.0	+
C6 ACTIVE ULCER	100.0	+	100.0	+

[a] CEAP = CEAP classification of chronic venous disease (Eklof 2004)
[b] Agreement = proportion of participants identified at the same grade of clinical disease by the same observer at two different examinations.
[c] Kappa statistic: <0.20 = poor, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = good, 0.81-1.00 = very good
- Kappa statistic could not be calculated as cross tabulation of CEAP class rated by the same observer on two different examinations was asymmetrical
+ Kappa statistic could not be calculated as there was no evidence of condition on examination 1 or 2.

TABLE 5.4 PREVALENCE OF CHRONIC VENOUS DISEASE AT FOLLOW UP, BASED ON EXAMINATION VERSUS PHOTOGRAPHIC CLASSIFICATION FOR 676 PARTICIPANTS

CEAP [a]	EXAMINATION N (%) [b]	PHOTOGRAPHS N (%) [b]	AGREEMENT (%) [d]	KAPPA [e]
C1 TELANGIECTASIA	495 (73.2%)	604 (89.3%)	60.9	0.34
Grade 1	341 (50.4%)	461 (68.2%)		
Grade 2	115 (17.0%)	125 (18.5%)		
Grade 3	39 (5.8%)	18 (2.7%)		
C1 RETICULAR VEINS	396 (58.6%)	519 (76.8%)	51.0	0.31
Grade 1	221 (32.7%)	321 (47.5%)		
Grade 2	139 (20.6%)	160 (23.7%)		
Grade 3	36 (5.3%)	38 (5.6%)		
C2 VARICOSE VEINS	293 (43.3%)	273 (40.4%)	80.0	0.66
Grade 1	166 (24.6%)	178 (26.3%)		
Grade 2	83 (12.3%)	66 (9.8%)		
Grade 3	44 (6.5%)	29 (4.3%)		

All measures based on 676 participants for whom photographs were available

[a] CEAP = CEAP classification of chronic venous disease (Eklof 2004)

[b] Classification of CVD based upon examination of the participant

[c] Classification of CVD based on photographic evidence

N (%) = number (%) of participants with CEAP class and Basle grade of disease

[d] Agreement = proportion of participants identified at the same grade of clinical disease between examination and photographic classification method

[e] Kappa statistic: <0.20 = poor, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = good, 0.81-1.00 = very good

TABLE 5.4 PREVALENCE OF CHRONIC VENOUS DISEASE AT FOLLOW UP, BASED ON EXAMINATION VERSUS PHOTOGRAPHIC CLASSIFICATION FOR 676 PARTICIPANTS (CONTINUED)

CEAP [a]	EXAMINATION N (%) [b]	PHOTOGRAPHS N (%) [c]	AGREEMENT (%) [d]	KAPPA [e]
C3 CORONA PHLEBECTATICA	32 (4.7%)	105 (15.6%)	83.9	0.29
C3 OEDEMA	28 (4.1%)	29 (4.3%)	96.6	0.58
C4a PIGMENTATION	34 (5.0%)	52 (7.7%)	94.4	0.53
C4a ECZEMA	13 (1.9%)	13 (1.9%)	99.4	0.84
C4b LIPODERMATOSCLEROSIS	9 (1.3%)	15 (2.2%)	98.5	0.58
C4b ATROPHIE BLANCHE	3 (0.4%)	2 (0.3%)	99.6	0.40
C5 HEALED ULCER	4 (0.6%)	7 (1.0%)	99.0	0.36
C6 ACTIVE ULCER	1 (0.1%)	1 (0.1%)	100.0	1.00

All measures based on 676 participants for whom photographs were available, except C3 corona phlebectatica which was based on 675 participants.

[a] CEAP = CEAP classification of chronic venous disease (Eklof 2004)

[b] Classification of CVD based upon examination of the participant

[c] Classification of CVD based on photographic evidence

N (%) = number (%) of participants with CEAP class and Basle grade of disease

[d] Agreement = proportion of participants identified at the same grade of clinical disease between examination and photographic classification method

[e] Kappa statistic: <0.20 = poor, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = good, 0.81-1.00 = very good

TABLE 5.5 INTER-OBSERVER RELIABILITY FOR VENOUS REFLUX MEASUREMENTS AT FOLLOW UP

	OBSERVERS 1 AND 2 (n=19)		OBSERVERS 3 AND 4 (n=30)		ALL OBSERVERS (n=49)	
VEIN SEGMENT	**AGREEMENT (%) [a]**	**KAPPA [b]**	**AGREEMENT (%) [a]**	**KAPPA [b]**	**AGREEMENT (%) [a]**	**KAPPA [b]**
CFV	94.7	-	100.0	+	98.0	-
FV ORIGIN	94.7	-	100.0	+	98.0	-
FV LOWER THIGH	94.7	-	100.0	+	97.9	-
POP ABOVE KNEE	94.7	-	93.3	0.63	93.9	0.54
POP BELOW KNEE	84.2	0.62	83.3	0.59	83.7	0.51
GSV ORIGIN	100.0	1.00	93.3	0.71	95.9	0.83
GSV LOWER THIGH	94.7	0.88	90.0	0.73	91.8	0.80
GSV UPPER CALF	78.9	0.55	80.0	0.52	79.6	0.54
GSV LOWER CALF	94.7	0.87	93.3	0.71	93.9	0.81
SSV	94.7	0.64	86.7	0.50	89.8	0.54

CFV = common femoral vein
FV = femoral vein
POP = popliteal vein
GSV origin = great saphenous vein
SSV = small saphenous vein
[a] Agreement = proportion of participants identified as having venous reflux ≥ 0.5s between observers
[b] Kappa statistic: <0.20 = poor, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = good, 0.81-1.00 = very good
- Kappa statistic could not be calculated as the presence of venous reflux ≥ 0.5s between the two observers was asymmetrical
+ Kappa statistic could not be calculated as there was no evidence of venous reflux ≥ 0.5 s for that vein segment on either examination by different observers

TABLE 5.6 INTRA OBSERVER RELIABILITY FOR VENOUS REFLUX MEASUREMENTS AT FOLLOW UP

	OBSERVER 1 (n=10)		OBSERVER 2 (n=9)		OBSERVER 3 (n=11)		OBSERVER 4 (n=19)	
VEIN SEGMENT	AGREEMENT (%) [a]	KAPPA [b]	AGREEMENT (%) [a]	KAPPA [b]	AGREEMENT (%) [a]	KAPPA [b]	AGREEMENT (%) [a]	KAPPA [b]
CFV	90.0	-	88.9	-	100.0	+	89.8	-
FV ORIGIN	100.0	+	100.0	+	100.0	+	100.0	+
FV LOWER THIGH	100.0	+	100.0	+	100.0	+	100.0	+
POP ABOVE KNEE	100.0	+	88.9	-	81.8	-	89.5	0.60
POP BELOW KNEE	100.0	+	88.9	-	90.9	-	78.9	0.22
GSV ORIGIN	90.0	0.62	100.0	1.00	90.9	0.74	89.5	0.64
GSV LOWER THIGH	90.0	0.74	88.9	0.77	100.0	1.00	88.9	0.60
GSV UPPER CALF	70.0	0.29	100.0	1.00	90.9	0.81	83.3	0.56
GSV LOWER CALF	80.0	-	100.0	1.00	72.7	0.54	77.8	0.20
SSV	90.0	-	100.0	1.00	100.0	+	84.2	0.08

CFV = common femoral vein
FV = femoral vein
POP = popliteal vein,
GSV = great saphenous vein
SSV = small saphenous vein
[a] Agreement = proportion of participants identified as having venous reflux ≥ 0.5s between observers
[b] Kappa statistic: <0.20 = poor, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = good, 0.81-1.00 = very good
- Kappa statistic could not be calculated as the presence of venous reflux ≥ 0.5s by the same observer on 2 different examinations was asymmetrical
+ Kappa statistic could not be calculated as there was no evidence of venous reflux ≥ 0.5 s for that vein segment on either examination by the same observer

CHAPTER 6: RESPONSE AND REPRESENTATIVENESS OF THE STUDY SAMPLE

6.1 CHAPTER OUTLINE

In health services research, it is important to ensure that study participants on whom data are obtained, are similar to individuals not in the study. If a representative sample is achieved, then the study findings can be extrapolated and generalised to the wider population. There are two issues in determining the generalisability of study results. Firstly, the study sample must be representative of the target population. In this study, the target population comprised the population of Edinburgh. Secondly, the study sample should be representative of the study population. In this follow up cohort, the study population comprised the 1,566 baseline participants.

This chapter begins by detailing the response to the follow up phase of the Edinburgh Vein Study. Categories of response are analysed by age and sex. Using demographic population data, comparisons are made to determine if the follow up study sample are representative of the Edinburgh population in terms of age, sex, social class and ethnicity. Participants of the follow up study are then compared to the study population at baseline. More specifically, lifestyle factors, medical history and symptoms, treatment and family history of CVD are compared between follow up participants and non-participants.

6.2 RECRUITMENT AND RESPONSE

The recruitment process of the follow up phase of the Edinburgh Vein Study is shown in Figure 6.1. The target study population comprised 1,566 participants who were examined at baseline. During the 13-year follow up period, 101 (6.4%) baseline participants died and 9 (0.6%) emigrated. Thus, 1,456 men and women were eligible to take part in the follow up study. Of these, 14 (0.9%) were identified as living in another health authority. The health authorities failed to provide the contact details of either the participant or their general practitioner, and these people were deemed "unable to trace".

Invitation letters were sent to the remaining 1442 baseline participants, of whom 172 (11.0%) replied and refused to take part in the follow up study ("refusals"). A further 321 (20.5%) baseline participants could not be reached despite two invitation letters, three attempts at contacting them by telephone and a subsequent re-check of their details on the Community Health Index register. These people were classified as "no response". The remaining 949 subjects agreed to participate but of these, 69 (4.4%) subsequently withdrew prior to their appointment, and were termed "withdrawals". This resulted in a final study sample of 880 participants, giving a response rate of 60.4% (880 out of 1,456). Of the 172 participants who refused to take part, 50 completed the refusal questionnaire. The most common reason for not taking part was that the individual did not have venous disease (58%), followed by lack of time (22%). Of the 50 who completed a questionnaire, 8 had venous disease, 4 of whom had previous surgery but felt there was no point in taking part in the study as varicose veins return despite treatment.

6.2.1 Response by age

Figure 6.2 displays the follow up response by age group at baseline. Non-participant refers to any baseline participant who was eligible to take part in the follow up study but did not participate. Non-participants include those who refused to take part, did not respond, withdrew or were unable to trace (n=576). Follow up study participants were older than non-participants (mean age 46.6 years vs. 41.8 years, $p<0.001$). Of the people who took part in the follow up study, 4.9% and 13.5% were aged 18-24 and 25-34 years at baseline compared to 12.7% and 22.7% of non-participants in these respective age groups. The proportion of participants and non-participants aged 35-44 years at baseline were similar (21.6% and 23.6% respectively). The greatest difference in response was that 32.3% of participants and 19.9% of non-participants were aged 45-54 years at baseline. Finally, 27.7% of participants and 23.1% of non-participants were aged between 55 and 64 years at baseline.

A more detailed analysis of the category of response by age at baseline is presented in Table 6.1. Participation was highest was in those aged 45-54 years at baseline, with 73.6% of participants in this age group at the initial stage of the study, examined at follow up. Those aged between 18 and 24 years at baseline were least likely to participate in the follow up study (37.1%). The refusal rate was highest in those aged 55-64 years (17.2%) and lowest in those aged 25-34 years at baseline (6.8%). The rate of no response was highest in those aged between 18 and 24 years at baseline (41.4%). Furthermore, this age group also had the highest withdrawal rate (8.6%) whilst the lowest was in those aged between 45 and 54 years at baseline (2.8%).

6.2.2 Response by sex

The response to follow up by sex is summarised in Table 6.2. Excluding 110 people who had died or emigrated, 1,456 baseline participants were eligible to take part in the follow up study. Of these, 43.5% were men and 56.5% were women. The response was similar in men and women, with 61.5% and 59.6% of male and female baseline participants agreeing to take part in the follow up study (p=0.46). The refusal rate was slightly higher in women than in men (13.3% and 9.9% respectively) (p=0.05). There were no significant differences between men and women with regards to the rate of no response (p=0.15) and the withdrawal rate (p=0.13). Similarly, while the numbers of men and women who were deemed "unable to trace" were small, there was no statistically significant difference between the two groups (p=0.95).

6.2.3 Social class

At baseline, social class was measured according to the occupation of the participants, using the Standard Occupational Classification (Office of Population Censuses and Surveys 1991). There were six categories of social class ranging from professional to skilled and unskilled work. Table 6.3 presents a summary of social class of the participants and non-participants of the follow up study. Data on social class was available for 782 participants and 504 non-participants. A higher proportion of participants were in social classes I and II, professional and managerial jobs respectively, while a higher proportion of non-participants were in social classes IIIM-V. When analysed by non-manual (I-IIIN) and manual (IIIM-V) labour, a significant difference was found between the two groups. Participants in the follow up study were more likely to be non-manual workers than non-participants (77.7% and 68.3% respectively) (p<0.001).

6.3 REPRESENTATIVENESS OF STUDY SAMPLE TO THE POPULATION OF EDINBURGH

Using population data from various sources, including the National Records of Scotland (NRS), Scottish Census (General Register Office for Scotland (GROS)), and Scottish Index of Multiple Deprivation (SIMD), the demographic characteristics of the follow up study participants are now compared to the general population residing in Edinburgh.

6.3.1 Age

The age of follow up study participants was compared to the age of the population of Edinburgh using the National Records of Scotland (last published, 19/05/2011). The age groups of participants had to be adjusted so that they matched the age groups quoted in the above publication. One of the age groups in the published distribution for Edinburgh was over 75 years. In our study, the maximum age of participants at baseline was 64 years. Given that the follow up period was 13 years, the eldest a study participant could be at follow up was 78 years. Therefore, proportionately there would be fewer study participants in this age group compared to Edinburgh.

The follow up study sample was significantly older than the population of Edinburgh [Figure 6.3]. The final study sample included a smaller proportion of people aged between 30-44 years (12.7%) than the proportion of people this age living in Edinburgh (23.0%). The proportion of participants and the population of Edinburgh aged between 45 and 59 years were 32.3% and 18.1% respectively. The difference in age was most marked for those aged 60-74 years, with 45.2% of participants aged in this group at follow up compared to just 12.1% of the population of Edinburgh. Finally, 9.8% of follow up study participants were aged over 75 years compared to 7.3% of people residing in Edinburgh.

6.3.2 Sex

According to the General Register Office for Scotland, figures published in 2011 showed that 48.4% of the population of Edinburgh were male and 51.6% were female. The EVS follow up participants included 390 men (44.3%) and 490 women (55.7%). Therefore, the study sample contained a higher proportion of women than the population of Edinburgh.

6.3.3 Social class

Social class of participants in the follow up study was compared to the population of Edinburgh. The postcodes of the 880 follow up study participants were linked to the Scottish Index of Multiple Deprivation (SIMD 2009), to generate a deprivation score for each participant based on the postcode where they resided. Deprivation scores were grouped into 5 quintiles according to the SIMD guidelines, with 1 being the most deprived and 5 being the least deprived. The quintiles for the 880 study participants were compared to the SIMD quintiles for 12,429 postcodes within the City of Edinburgh. The results are presented in Figure 6.4. Participants in the follow up study tended to be less deprived than the population of Edinburgh, although the difference was not significant (52.2% of study participants were classified in the least deprived group, while the corresponding proportion for the population of Edinburgh was 44.1%). When social class was analysed as a continuous variable, no difference was found with the mean quintile of Edinburgh Vein Study follow up participants 3.9 compared to 3.7 in the population of Edinburgh (p=0.18).

6.3.4 Ethnic group

Of the 880 participants in the follow up study, 99.5% were Caucasian, 0.1% Indian, 0.2% Chinese and 0.1% mixed race. At the 2001 Scottish Census, published by the General Register Office for Scotland (GROS), 95.9% of the population of Edinburgh were Caucasian, 0.5% Indian, 0.8% Chinese and 0.6% mixed race. Therefore the study sample was representative of the population of Edinburgh in terms of ethnic groups.

6.4 REPRESENTATIVENESS OF THE STUDY SAMPLE TO THE STUDY POPULATION

To measure the representativeness of the EVS follow up study sample to the study population, data from baseline will be compared between participants and non-participants of the follow up study. Lifestyle factors such as body mass index, medical history of clinical risk factors, smoking and mobility at work will be examined. Social class will then be compared. Finally, CVD at baseline, including severity and symptoms of disease, previous treatment, family history and prevalence of venous reflux are presented.

6.4.1 Body mass index

There was no significant difference between participants and non-participants in terms of BMI at baseline. Follow up study participants had a mean BMI of 25.6 kg/m^2 at baseline compared to 25.4 kg/m^2 in non- participants (p=0.22). The proportion of participants and non-participants who were normal weight (51% and 52%), overweight (37% and 36%) and obese (12% and 12%) were also similar (p=0.62).

6.4.2 Medical history

Medical history of associated venous diseases and possible clinical risk factors at baseline are presented in Table 6.4. Participants were more likely to have suffered haemorrhoids at baseline (32.2% compared to 22.6% of non-participants ($p<0.001$). The occurrence, at baseline, of other possible medical risk factors for CVD, including deep vein thrombosis, pulmonary embolism, hernia, phlebitis, fractured leg or swollen legs post operatively or post pregnancy, did not differ significantly between participants and non-participants in the follow up study (all $p \geq 0.05$).

6.4.3 Smoking

Smoking status at baseline was compared in participants and non-participants. Of the participants in the follow up study, 80.3% were non-smokers at baseline compared to 65.8% of non-participants ($p<0.001$). Smoking was split into three groups according to the following status at baseline: current smoker, ex-smoker and never smoked, the results of which are presented in Figure 6.5. Results show that participants in the follow up study were more likely to have given up smoking or indeed, never smoked at the baseline stage of the study than those who did not participate in the follow up study.

6.4.4 Mobility at work

At baseline, participants were asked to record the proportion of time spent sitting, standing, walking or heavy lifting as never, up to half or over half the working day. Results were compared between participants and non-participants in the follow up study. No significant differences were found in the amount of time spent sitting, standing or walking at work (all $p \geq 0.05$). However, participants in the follow up study spent less time doing work which involved heavy lifting (23.3%) compared to non-participants (26.3%). Moreover, 4.7% of participants spent over half the day doing heavy work at baseline compared to 6.5% of non-participants ($p=0.03$). This observation could be explained by the fact that, according to the social class based on occupation, participants were less likely to be manual workers than non-participants.

6.4.5 Severity of chronic venous disease

Baseline data on the classification of CVD was compared between participants and non-participants in the follow up study. The results of this comparison are displayed in Table 6.5. From the data it is evident that there is little difference in the distribution of CVD between participants and non-participants, except that slightly more non-participants were free of telangiectases and reticular veins. Of the follow up study participants, 92.1% had evidence of telangiectases at baseline compared to 86.2% of non-participants ($p=0.01$). The same was true for reticular veins, with 90.2% of follow up participants presenting with this condition at baseline compared to 86.6% of non-participants ($p=0.02$). There were no significant differences between the baseline prevalence of varicose veins ($p=0.40$) or CVI ($p=0.82$) in participants and non-participants of the follow up study.

6.4.6 Symptoms of chronic venous disease

Symptoms of CVD measured in the baseline questionnaire, were compared between participants and non-participants of the follow up study [Table 6.6]. There were no significant differences in the frequencies of these symptoms at baseline between those who did and did not take part in the follow up study.

6.4.7 Previous treatment for chronic venous disease

Participants in the follow up study were more likely to have had previous surgery for varicose veins than non-participants (7.8% and 4.5% respectively) (p=0.02). The same was true for sclerotherapy, with 4.6% of participants reporting this treatment at baseline compared to 2.6% of non-participants (p=0.04).

6.4.8 Family history of chronic venous disease

Family history of CVD was defined as varicose veins or venous ulceration in any one of the mother, father, grandparents or siblings at the baseline stage of the study. Family history of CVD did not differ significantly between participants and non-participants of the follow up study. Sixty two per cent of those of who took part in the follow up study reported a family history of CVD at baseline compared to 58.7% of non-participants (p=0.19).

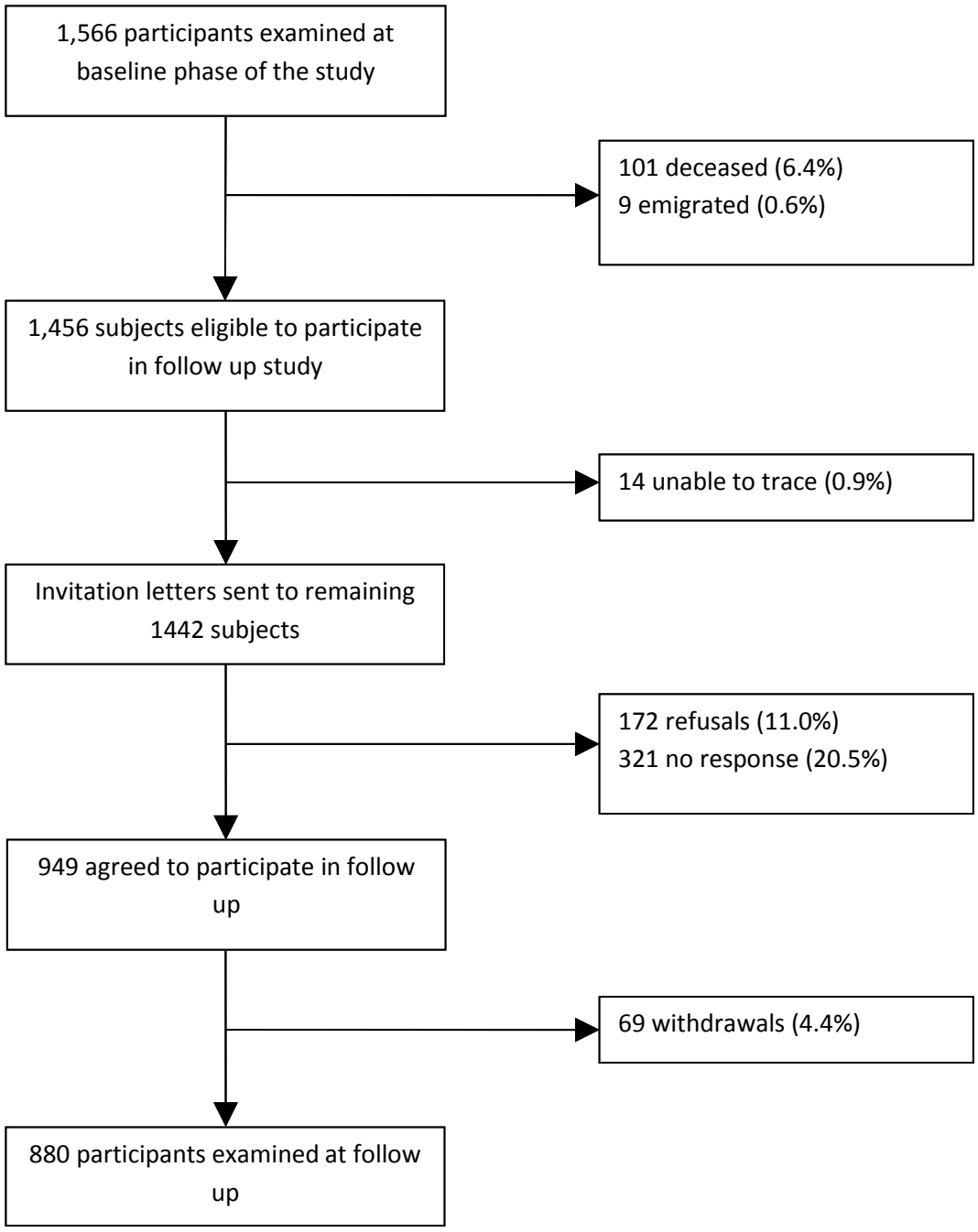
6.4.9 Venous reflux

Figure 6.5 displays the prevalence of reflux at baseline, in participants and non-participants of the follow up study. Venous reflux was defined as reflux ≥ 0.5 seconds in any one of the veins assessed. Deep system reflux comprised reflux in any one of the CFV, FV and POP veins while superficial system reflux comprised reflux in the GSV or SSV. If a participant had reflux in a deep and superficial vein, they were classified as having reflux in both systems. There were no significant differences in the prevalence of reflux in the deep (p=0.32), superficial (p=0.75) and combined systems (p=0.58) between participants and non-participants of the follow up study.

6.5 CHAPTER SUMMARY

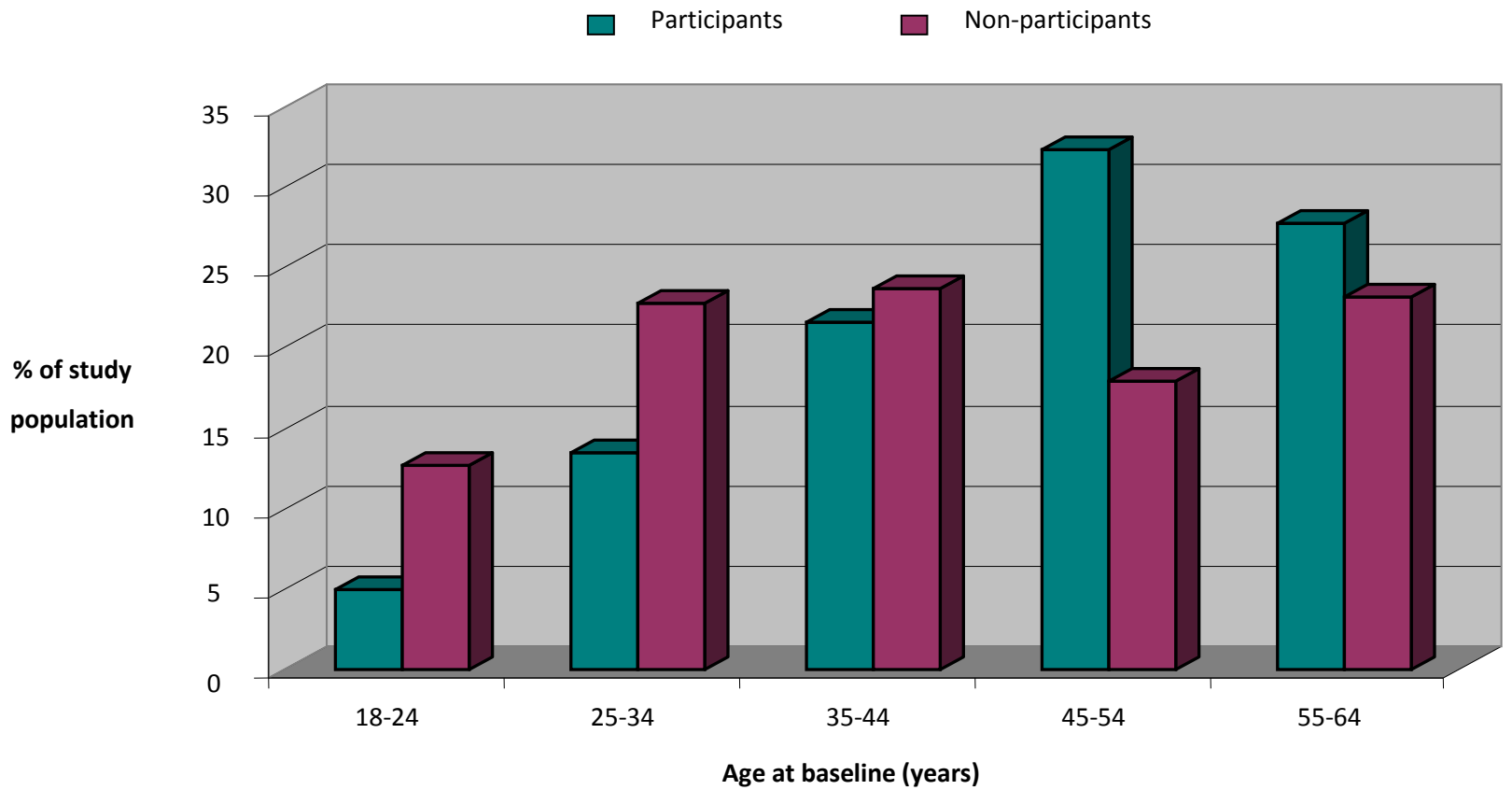
The response rate for the follow up phase of the Edinburgh Vein Study was 60.4% and was similar in men and women. Follow up study participants tended to be older than both non-participants, and the population of Edinburgh. The study sample contained a higher proportion of women than the proportion of females in Edinburgh. Participants were similar to the population of Edinburgh in terms of social class. However, those who took part in the follow up study were more likely to have non-manual jobs. There were no differences in the baseline prevalence of varicose veins or CVI between participants and non-participants, but the former reported a higher rate of varicose vein treatment at baseline, including both surgery and sclerotherapy. Furthermore participants of the follow up study were also more likely to have had haemorrhoids at baseline. Finally, those who took part in the follow up study were more likely to be non-smokers than those who did not take part.

FIGURE 6.1 RECRUITMENT IN THE FOLLOW UP OF THE EDINBURGH VEIN STUDY



Unable to trace = baseline study participants who had moved to another health authority and whose address could not be traced.
Refusals = baseline study participants who replied and refused to take part in the follow up study.
No response = baseline study participants who did not reply despite 2 invitation letters and 3 attempts to contact them by telephone.
Withdrawals = baseline study participants who initially agreed to participate in the follow up study but subsequently withdrew or failed to attend

FIGURE 6.2 AGE DISTRIBUTION OF PARTICIPANTS AND NON-PARTICIPANTS IN THE EDINBURGH VEIN STUDY FOLLOW UP BY AGE AT BASELINE



Participants = baseline participants who took part in the follow up study and underwent clinical examination (n=880)
Non-participants = baseline participants who did not take part in the follow up study i.e. refusals + no response + withdrawals + unable to trace (n= 576)

TABLE 6.1 CATEGORIES OF RESPONSE TO THE EDINBURGH VEIN STUDY FOLLOW UP BASED ON AGE DISTRIBUTION AT BASELINE

	CATEGORIES OF RESPONSE					
AGE GROUP BASELINE (YEARS)	**EXAMINED N (%)**	**REFUSALS N (%)**	**NO RESPONSE N (%)**	**WITHDRAWAL N (%)**	**UNABLE TO TRACE N (%)**	**TOTAL N (%)**
18-24	43 (37.1)	11 (9.5)	48 (41.4)	10 (8.6)	4 (3.4)	116 (8.0)
25-34	120 (48.0)	17 (6.8)	91 (36.4)	15 (6.0)	7 (2.8)	250 (17.2)
35-44	189 (58.0)	33 (10.1)	85 (26.1)	18 (5.5)	1 (0.3)	326 (22.4)
45-54	285 (73.6)	46 (11.9)	44 (11.4)	11 (2.8)	1 (0.3)	387 (26.6)
55-64	243 (64.4)	65 (17.2)	53 (14.1)	15 (4.0)	1 (0.3)	377 (25.9)
TOTAL	880 (60.4)	172 (11.8)	321 (22.0)	69 (4.8)	14 (1.0)	1456 (100)

N (%) = number and percentage within each group based on response at follow up
Examined = baseline study participants who agreed to take part in the follow up study and underwent clinical examination
Refusals = baseline study participants who replied and refused to take part in the follow up study.
No response = baseline study participants who did not reply despite 2 invitation letters and 3 attempts to contact them by telephone.
Withdrawals = baseline study participants who initially agreed to participate in the follow up study but subsequently withdrew or failed to attend.
Unable to trace = baseline study participants who had moved to another health authority and whose address could not be traced.

TABLE 6.2 CATEGORIES OF RESPONSE TO THE EDINBURGH VEIN STUDY FOLLOW UP BASED ON SEX

CATEGORY OF RESPONSE	MALES N (%)	FEMALES N (%)	TOTAL N (%)	P VALUE*
EXAMINED	390 (61.5)	490 (59.6)	880 (60.4)	0.46
REFUSALS	63 (9.9)	109 (13.3)	172 (11.8)	0.05
NO RESPONSE	151 (23.8)	170 (20.7)	321 (22.0)	0.15
WITHDRAWALS	24 (3.8)	45 (5.5)	69 (4.7)	0.13
UNABLE TO TRACE	6 (1.0)	8 (0.9)	14 (1.0)	0.95
TOTAL	634 (43.5)	822 (56.5)	1456 (100)	-

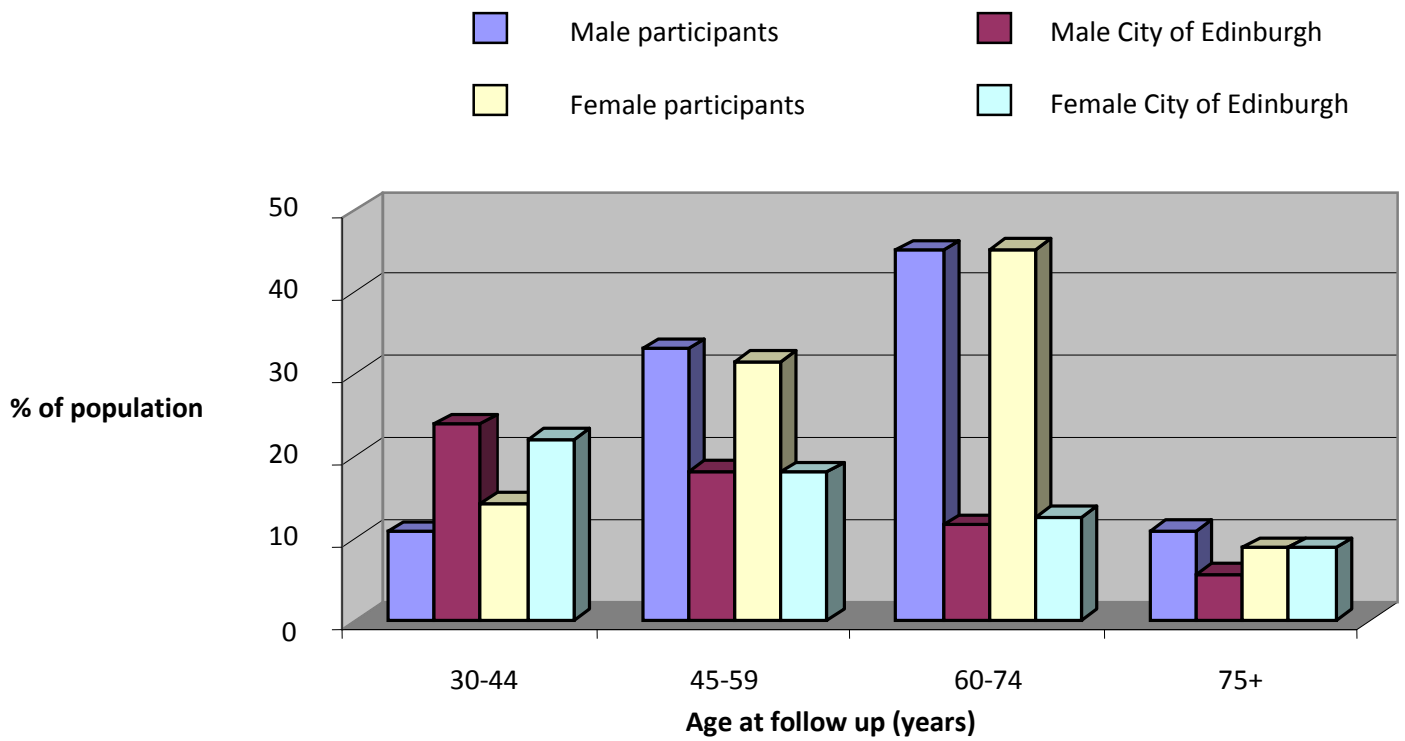
N (%) = number and percentage within each sex based on category of response at follow up
Examined = baseline study participants who agreed to take part in the follow up study and underwent clinical examination
Refusals = baseline study participants who replied and refused to take part in the follow up study
No response = baseline study participants who did not reply despite 2 invitation letters and 3 attempts to contact them by telephone
Withdrawals = baseline study participants who initially agreed to participate in the follow up study but subsequently withdrew or failed to attend
Unable to trace = baseline study participants who had moved to another health authority and whose address could not be traced
* P value based on chi square test for differences in category of response between men and women

TABLE 6.3 SOCIAL CLASSES OF PARTICIPANTS AND NON-PARTICIPANTS IN THE EDINBURGH VEIN STUDY FOLLOW UP, AS DETERMINED AT BASELINE

SOCIAL CLASS AT BASELINE *	PARTICIPANTS N (%)	NON-PARTICIPANTS N (%)	TOTAL N (%)
SOCIAL CLASS I [a]	84 (10.7)	49 (9.7)	133 (10.3)
SOCIAL CLASS II [a]	335 (42.8)	156 (30.9)	491 (38.2)
SOCIAL CLASS IIIN [a]	189 (24.2)	139 (27.6)	328 (25.5)
SOCIAL CLASS IIIM [b]	101 (12.9)	89 (17.7)	190 (14.8)
SOCIAL CLASS IV [b]	46 (5.9)	40 (7.9)	86 (6.7)
SOCIAL CLASS V [b]	27 (3.5)	31 (6.2)	58 (4.5)
TOTAL	782	504	1286

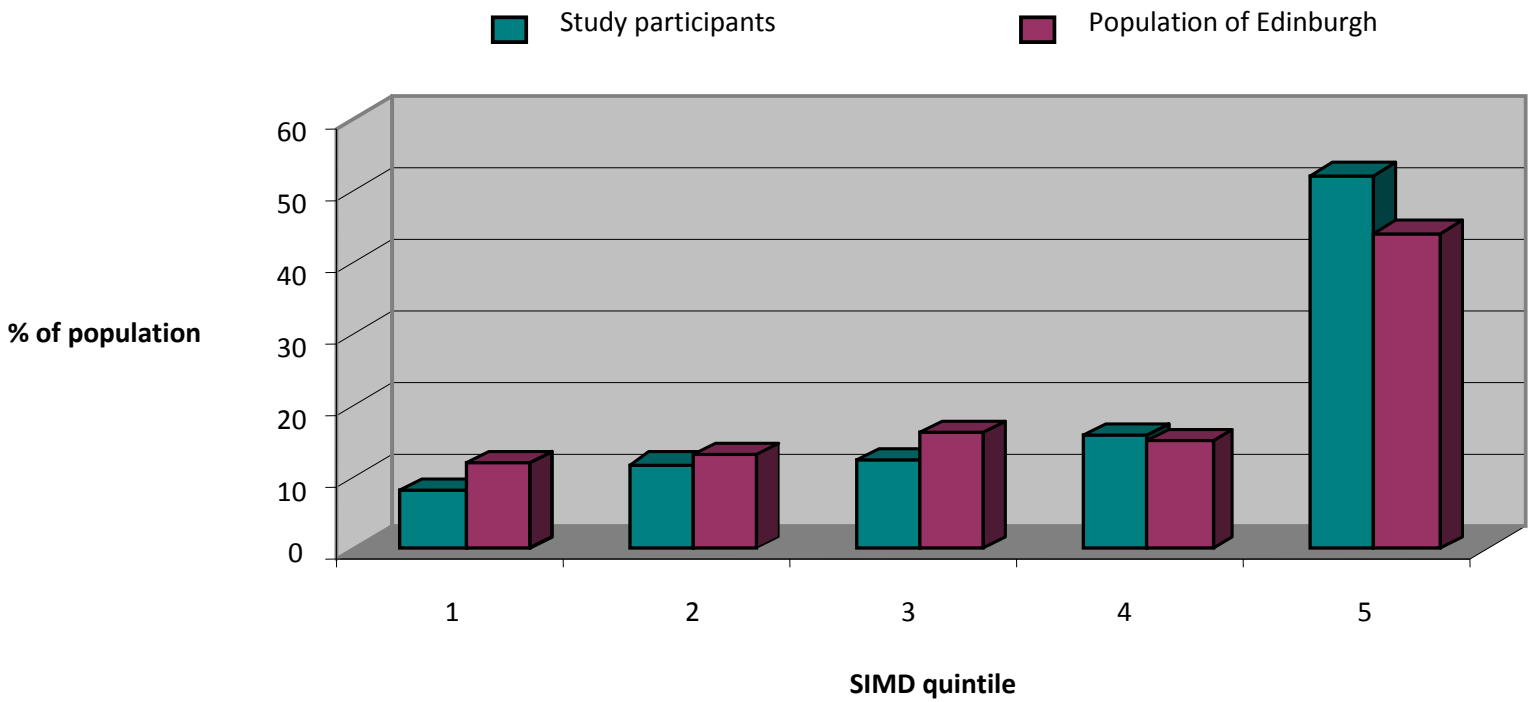
N (%) = number and percentage within each group based on social class at baseline
Participants = baseline participants who took part in the follow up study and underwent clinical examination (n=880)
Non-participants = baseline participants who did not take part in the follow up study i.e. refusals + no response + withdrawals + unable to trace (n= 576)
[*] Social class determined at baseline using the Standard Occupational Classification (Office of Population Censuses and Surveys, 1991)
[a] Social classes I-IIIN = non-manual workers
[b] Social classes IIIM-V = manual workers

FIGURE 6.3 AGE AND SEX DISTRIBUTION FOLLOW UP STUDY PARTICIPANTS COMPARED TO THE POPULATION OF EDINBURGH



Participants = baseline participants who took part in the follow up study and underwent clinical examination (n=880)
Non-participants = baseline participants who did not take part in the follow up study i.e. refusals + no response + withdrawals + unable to trace (n= 576)

FIGURE 6.4 DEPRIVATION SCORES FOR EDINBURGH VEIN STUDY FOLLOW UP PARTICIPANTS AND THE POPULATION OF EDINBURGH.



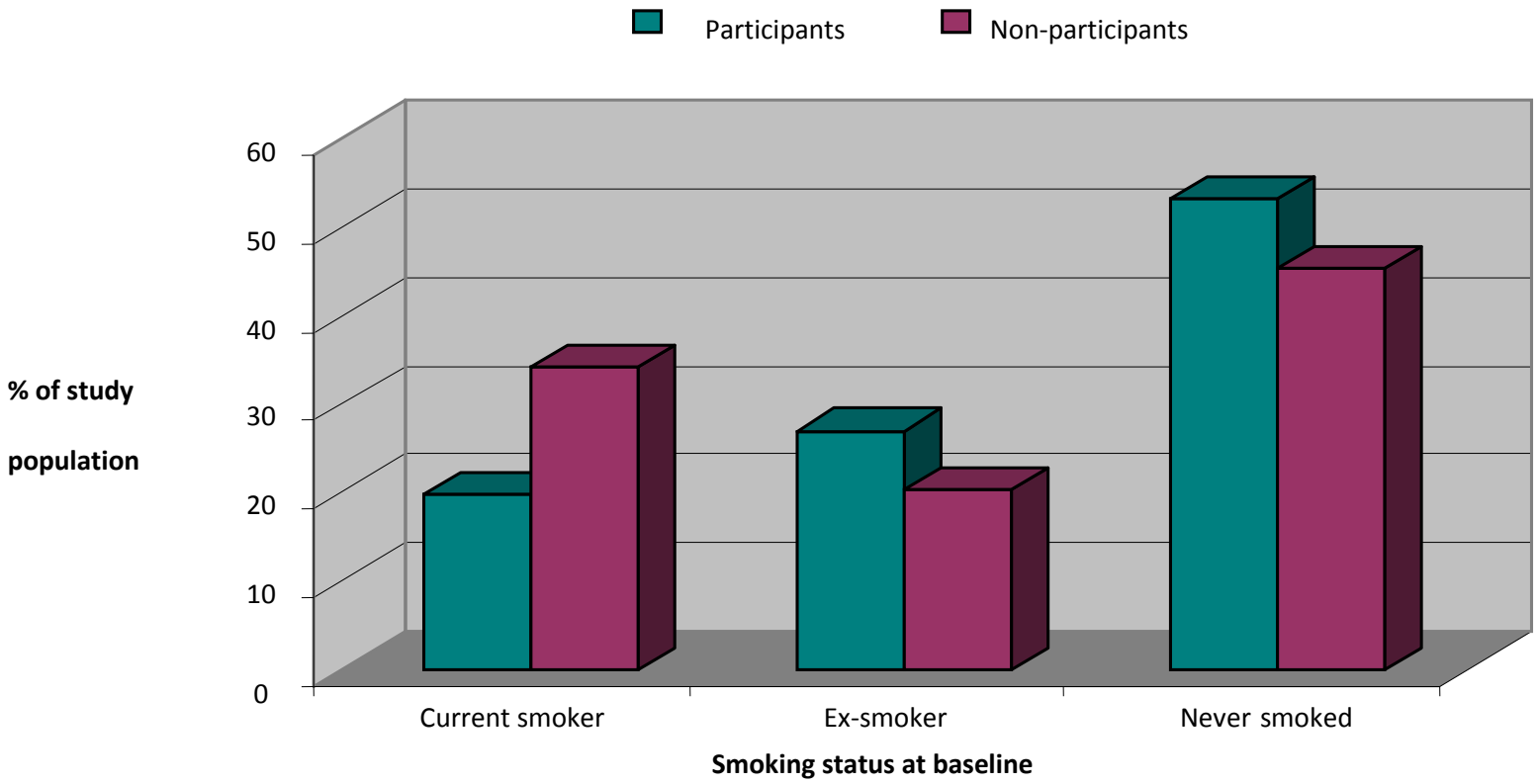
SIMD quintile: 1=most deprived and 5=least deprived

TABLE 6.4 HISTORY OF MEDICAL RISK FACTORS AT BASELINE, IN PARTICIPANTS AND NON-PARTICIPANTS OF THE EDINBURGH VEIN STUDY FOLLOW UP

HISTORY OF MEDICAL RISK FACTORS	PARTICIPANTS N (%)	NON-PARTICIPANTS N (%)	P-VALUE*
DEEP VEIN THROMBOSIS	22 (2.5)	9 (1.6)	0.23
HERNIA	53 (6.0)	23 (4.0)	0.09
PULMONARY EMBOLISM	5 (0.6)	6 (1.0)	0.36
FRACTURED LEG	81 (9.3)	43 (7.5)	0.24
SWOLLEN LEG POST-OPERATIVELY	53 (6.3)	25 (4.5)	0.17
SWOLLEN LEG POST-PREGNANCY	140 (36.3)	96 (44.0)	0.06
PHLEBITIS	41 (4.7)	16 (2.8)	0.07
HAEMORRHOIDS	283 (32.2)	130 (22.6)	<0.001

N (%) = number and percentage within each group with condition at baseline
Participants = baseline participants who took part in the follow up study and underwent clinical examination (n=880)
Non-participants = baseline participants who did not take part in the follow up study i.e. refusals + no response + withdrawals + unable to trace (n= 576)
*P value from chi square test for differences in medical history at baseline between participants and non-participants in the follow up study

FIGURE 6.5 SMOKING STATUS AT BASELINE IN PARTICIPANTS AND NON-PARTICIPANTS OF THE EDINBURGH VEIN STUDY FOLLOW UP



Participants = baseline participants who took part in the follow up study and underwent clinical examination (n=880)
Non-participants = baseline participants who did not take part in the follow up study i.e. refusals + no response + withdrawals + unable to trace (n= 576)

TABLE 6.5 CATEGORIES AND SEVERITY OF CEAP CHRONIC VENOUS DISEASE AT BASELINE IN PARTICIPANTS AND NON-PARTICIPANTS OF THE EDINBURGH VEIN STUDY FOLLOW UP

CEAP [a]	PARTICIPANTS N (%)	NON-PARTICIPANTS N (%)	P VALUE*
C1 TELANGIECTASES [b]	811 (92.1)	497 (86.2)	0.01
Grade 1	740 (84.1)	455 (79.0)	
Grade 2	68 (7.7)	40 (6.9)	
Grade 3	3 (0.3)	2 (0.3)	
C1 RETICULAR VEINS [b]	794 (90.2)	499 (86.6)	0.02
Grade 1	746 (84.8)	476 (82.6)	
Grade 2	48 (5.4)	23 (4.0)	
Grade 3	0 (0)	0 (0)	
C2 VARICOSE VEINS [b]	324 (36.8)	189 (32.8)	0.40
Grade 1	270 (30.7)	152 (26.4)	
Grade 2	51 (5.8)	30 (5.2)	
Grade 3	3 (0.3)	7 (1.2)	
C3-C6 CVI			
C3 [c]	49 (5.6)	33 (5.7)	0.82
C4 [d]	11 (1.3)	6 (1.0)	
C5-C6 [e]	4 (0.5)	4 (0.7)	

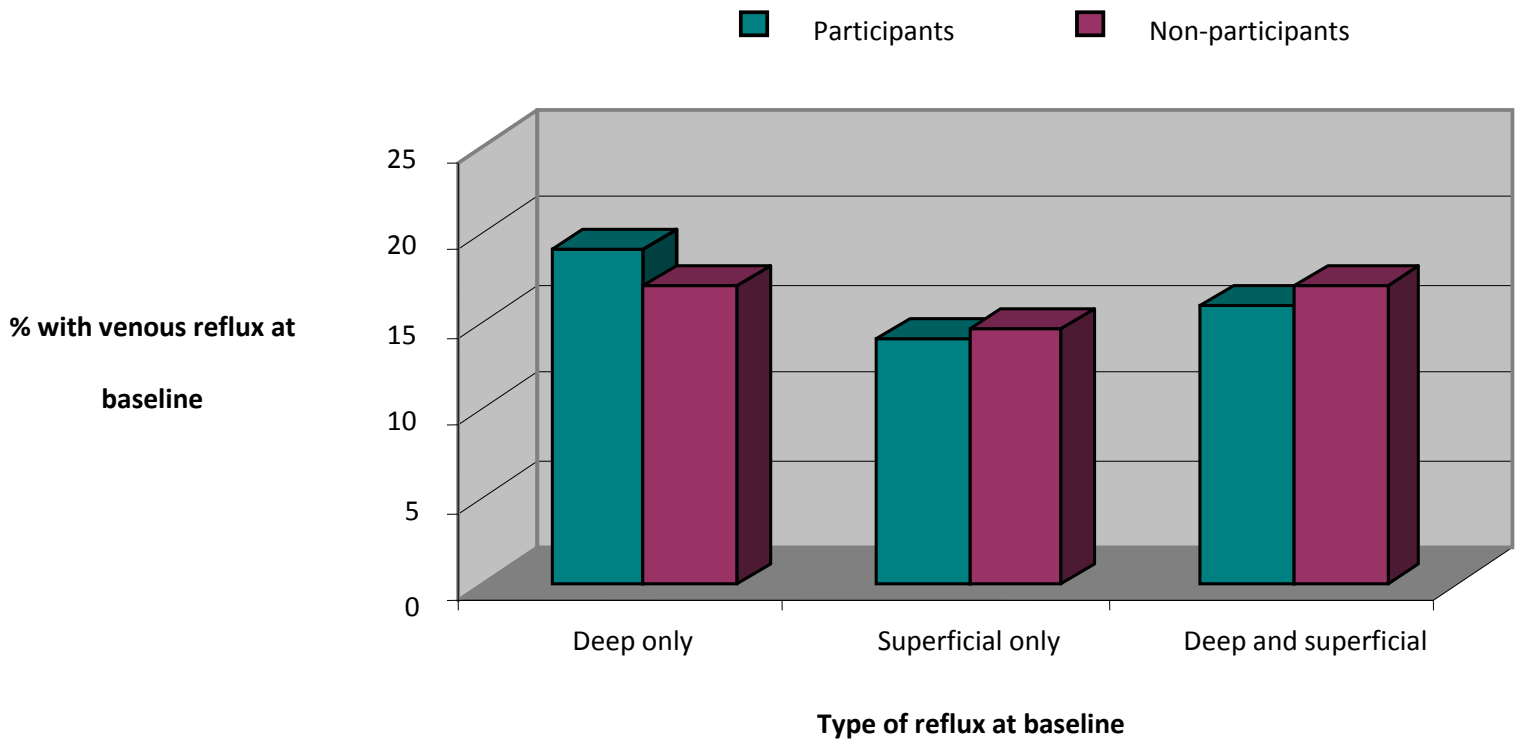
[a] CEAP = CEAP classification of chronic venous disease (Eklof 2004)
N (%) = number and percentage within each group with CEAP class and severity of venous disease at baseline
Participants = baseline participants who took part in the follow up study and underwent clinical examination (n=880)
Non-participants = baseline participants who did not take part in the follow up study i.e. refusals + no response + withdrawals + unable to trace (n= 576)
[b] Grade based on Basle classification for severity: 1 (mild), 2 (moderate) and 3 (severe)
[c] C3 CEAP = corona phlebectatica and venous oedema
[d] C4 CEAP = C4a pigmentation, C4a venous eczema, C4b lipodermatosclerosis and C4b atrophie blanche
[e] C5-C6 CEAP = C5 healed and C6 active venous ulceration
*P value from chi square linear trend test for differences in prevalence of CVD by participants and non-participants in the follow up study.

TABLE 6.6 SYMPTOMS OF CHRONIC VENOUS DISEASE, MEASURED AT BASELINE, IN PARTICIPANTS AND NON-PARTICIPANTS OF THE EDINBURGH VEIN STUDY FOLLOW UP

SYMPTOMS OF CVD AT BASELINE	PARTICIPANTS N (%)	NON-PARTICIPANTS N (%)	P-VALUE*
HEAVY LEGS	190 (21.6)	144 (25.1)	0.13
SWOLLEN LEGS	160 (18.2)	85 (14.9)	0.09
ACHING LEGS	375 (42.8)	260 (45.4)	0.33
RESTLESS LEGS	248 (28.2)	159 (27.7)	0.81
NIGHT CRAMPS	328 (37.4)	224 (39.0)	0.54
ITCHING	196 (22.3)	127 (22.1)	0.94
TINGLING	153 (17.4)	106 (18.4)	0.62

N (%) = number and percentage within each group reporting symptoms of CVD at baseline
Participants = baseline participants who took part in the follow up study and underwent clinical examination (n=880)
Non-participants = baseline participants who did not take part in the follow up study i.e. refusals + no response + withdrawals + unable to trace (n= 576)
*P value from chi square test for differences in symptoms of CVD at baseline between participants and non-participants in the follow up study.

FIGURE 6.6 VENOUS REFLUX ≥ 0.5 SECONDS DURATION MEASURED AT BASELINE, IN PARTICIPANTS AND NON-PARTICIPANTS OF THE EDINBURGH VEIN STUDY FOLLOW UP



Participants = baseline participants who took part in the follow up study and underwent clinical examination (n=880)
Non-participants = baseline participants who did not take part in the follow up study i.e. refusals + no response + withdrawals + unable to trace (n= 576)
Reflux = reverse blood flow ≥ 0.5 seconds. Deep reflux = common femoral, femoral or popliteal vein reflux. Superficial reflux = great or small saphenous vein reflux

CHAPTER 7: PREVALENCE AND INCIDENCE OF CHRONIC VENOUS DISEASE

7.1 CHAPTER OUTLINE

This chapter presents the prevalence and incidence of CVD from the Edinburgh Vein Study (EVS) follow up. Firstly prevalence of CVD at follow up will be reported and compared to the prevalence at baseline, to examine changes during the two stages of the study. Prevalence of CVD at follow up by sex, age, right or left leg and social class will also be explored. Incidence of varicose veins and CVI at follow up will then be presented by sex, age, left or right leg and social class. In this thesis, the prevalence and incidence of CVD is based on the clinical examination with adjustments made based on photographic evidence, as previously discussed in Chapter 5.

7.2 PREVALENCE OF C1-C6 CHRONIC VENOUS DISEASE AT FOLLOW UP

The prevalence of a disease is the total number of cases of disease in the population at a given time, divided by the number of individuals in the population. The prevalence in the Edinburgh Vein Study is the number of participants with evidence of CVD at follow up, divided by the number of participants who took part in both the baseline and follow up stages of the study. The leg assigned the highest CEAP class or Basle grade for severity of CVD was used for each participant.

7.2.1 Prevalence of C1-C6 chronic venous disease at baseline and follow up

The prevalence of C1-C6 CVD at the baseline and follow up are shown in Table 7.1. At follow up, fewer participants had C1 telangiectases and reticular veins than at baseline. Although the number of participants with grade 2 and 3 telangiectases increased, the overall prevalence of telangiectases decreased from 92.2% (95% CI 90.2-93.8) to 85.2% (95% CI 82.7-87.4) ($p<0.001$). The prevalence of grade 2 and 3 reticular veins also increased, but the overall prevalence decreased from 90.2% (95% CI 88.1-92.0) at baseline to 70.1% (95% CI 67.0-73.1) at follow up. The prevalence of C2 varicose veins increased slightly from 36.9% (95% CI 33.8-40.2) at baseline to 39.2% (95% CI 36.0-42.5) at follow up ($p<0.001$). There were fewer mild C2 varices at follow up and more classed as moderate to severe.

The prevalence of C3 corona phlebectatica increased almost three fold, from 5.9% (95% CI 4.5-7.7) at baseline to 16.7% (95% CI 14.4-19.3) at follow up ($p<0.001$). On the other hand, the prevalence of C3 oedema decreased from 11.6% (95% CI 9.6-13.9) at baseline to 4.4% (95% CI 3.3-6.0) at follow up ($p<0.001$). C4a pigmentation showed a statistically significant increase from 1.3% (95% CI 0.7-2.2) at baseline to 5.5% (95% CI 4.1-7.2) at follow up ($p<0.001$). Other C4 CEAP conditions including C4a venous eczema, C4b lipodermatosclerosis and C4b atrophie blanche were also more prevalent at follow up, although the increase was not statistically significant (all $p\geq0.05$). The prevalence of both C5 healed and C6 active venous ulceration increased from baseline to follow up, although the numbers are too small to estimate the prevalence of these conditions with precision.

7.2.2 Prevalence of C2 varicose veins and C3-C6 CVI by age

The prevalence of C2 varicose veins according to age at follow up is shown in Table 7.2. For all participants, regardless of sex, the prevalence of C2 varices increased linearly with age from 14.3% (95% CI 4.0-40.0) in those aged 25-34 years to 50.6% (95% CI 45.3-55.9) in those aged over 65 years at follow up (P trend<0.001). When analysed by sex, the prevalence of C2 varices increased linearly with age for male participants from 15.4% (95% CI 7.3-29.7) in those aged 35-44 years to 47.4% (95% CI 39.6-55.3) in those aged 65 years and older (P trend<0.001). For female participants, the prevalence also increased linearly with age (P trend<0.001) but only from aged 45 years onwards.

Table 7.3 shows that, with the exception of those aged 35-44 years, the overall prevalence of C3-C6 CVI increased linearly with age (P trend<0.001). The prevalence in participants aged over 65 years was 32.6% (95% CI 27.9-37.8), four times higher than in those aged 25-34 years, (7.1%, 95% CI 1.3-31.5). It should be noted only 4 of the 102 participants aged younger than 45 years had C3-C6 CVI at follow up. Therefore, the sample is too small to determine the prevalence of CVI in these age groups with precision. When analysed by gender, the prevalence of C3-C6 CVI remained significantly associated with age for both males and females. The prevalence increased from 12.3% (95% CI 6.9-21.3) in men aged 45-54 years to 36.8% (95% CI 29.6-44.8) in men aged 65 years and older (P trend<0.001). In women the prevalence of CVI rose from 10.8% (95% CI 5.8-19.3) in those aged 45-54 years to 29.3 (95% CI 23.2-36.1) in those aged 65 years and older (P trend<0.001).

7.2.3 Prevalence of C1-C6 chronic venous disease by sex

Table 7.4 displays the prevalence of C1-C6 CVD at follow up in male and female participants. The prevalence of C1 telangiectases was significantly higher in women (90.2%, 95% CI 87.3-92.5) than in men (79.0%, 95% CI 74.7-82.7) ($p<0.001$). Men had a higher prevalence of mild (grade 1) telangiectases ($P=0.001$) but women had a higher prevalence of moderate (grade 2) and severe (grade 3) telangiectases (both $p\leq0.001$). There was no significant sex difference in the overall prevalence of C1 reticular veins ($p=0.11$). However, moderate (grade 2) reticular veins were more common in women ($p=0.02$). The prevalence of C2 varicose veins was similar in men (40%, 95% CI 35.3-44.5) and women (38.6%, 95% CI 34.4-42.9) ($p=0.67$). When analysed by severity, no significant sex differences emerged for C2 varicose veins (all $p>0.05$).

The prevalences of C3 CVI conditions including corona phlebectatica and venous oedema, were similar between men and women (both $p>0.05$). Furthermore, there were no significant differences in the prevalences of C4 conditions by sex (all $p>0.05$). The prevalence of C5 healed ulceration was identical: 0.8% (95% CI 0.2-2.2) in men and 0.8 (95% CI 0.3-2.1) in women ($p=0.62$). The prevalence of C6 active ulceration was 0.1% (95% CI 0.1-0.6), with only one male participant presenting with this at the follow up examination ($p=0.44$). The number of cases of C4b atrophie blanche, C5 healed and C6 active venous ulceration in the study sample is very small and therefore the prevalence of these conditions cannot be estimated with precision.

7.2.4 Prevalence of C2 varicose veins and C3-C6 CVI by leg

The prevalence of unilateral and bilateral C2 varices at follow up was 20.1% (95% CI 17.6-22.9) and 19.1% (95% CI 16.6-21.8) respectively. C2 varices of any severity were more prevalent in the left leg, 29.6% (95% CI 26.7-32.8) than the right leg, 28.7% (95% CI 25.9-31.8) ($p<0.001$) [Table 7.5]. When analysed by severity, mild varicose veins were more common in the left leg ($p<0.001$) while moderate varicose veins had a higher prevalence in the right leg ($p<0.001$). The prevalence of severe varicose veins was similar in the right and left legs ($p=0.57$). There were no significant sex differences in the prevalence of C2 varices by leg. The prevalence in the right leg was 30.8% (95% CI 26.4-35.5) in men and 27.1% (95% CI 23.4-31.3) in women ($p=0.24$) and the left leg was 29.5% (95% CI 25.2-34.2) and 29.8% (95% CI 25.9-34.0) in men and women respectively ($p=0.92$).

The prevalence of unilateral and bilateral C3-C6 CVI at follow up was 6.9% (95% CI 5.4-8.8) and 13.7% (95% CI 11.6-16.2) respectively. When all classes of CVI were grouped together, the prevalence was higher in the left leg, 17.6% (95% CI 15.2-20.3) than in the right, leg 16.7% (95% CI 14.4-19.3) ($p<0.001$) [Table 7.5]. When CVI was split by classes, C3 CVI (corona phlebectatica and oedema), was more prevalent in the left leg ($p<0.001$). For C4-C6 CVI, no significant differences were found with regards to prevalence by leg (all $p\geq0.05$). There were no significant sex differences in the prevalence of CVI by leg. Of the male participants, 18.2% (95% CI 14.7-22.3) had CVI in their right leg at follow up compared to 15.5% (95% CI 12.6-19.0) of women ($p=0.29$). For the left leg, 18.2% (95% CI 14.7-22.3) of men compared to 17.1% (95% CI 14.1-20.7) of women had CVI at the follow up examination ($p=0.68$).

7.2.5 Prevalence of C2 varicose veins and C3-C6 CVI by social class

The prevalence of C2-C6 venous disease at follow up by social class, determined at baseline, is shown in Table 7.6. The prevalence of C2 varices was lowest in professional occupations, (33.3%, 95% CI 24.2-43.9) and highest in unskilled workers (51.9%, 95% CI 34.0-69.3). Merging the six social classes into two groups based on non-manual and manual occupations, did not produce any statistically significant difference, with prevalences of 38.2% (95% CI 34.4-42.1) and 42.0% (95% CI 34.5-49.4) respectively (p=0.37). There was no difference in the prevalence of CVI by social class (p=0.79).

7.3 INCIDENCE OF C2 VARICOSE VEINS AND C3-C6 CVI AT FOLLOW UP

The incidence of a disease is the number of new cases arising in a given period of time, in a population initially free of disease. In this study, the incidence of C2 varicose veins is the number of new cases of C2 varices at follow up, divided by the number of participants free of C2 varices at baseline. Similarly, the incidence of C3-C6 CVI is the number of new cases of C3-C6 CVI divided by those free of C2 varices and C3-C6 CVI at baseline. Participants with C2 varices at baseline but C3-C6 CVI at follow up are not included in the incidence of C3-C6 CVI as they are not cases of new venous disease but whose existing venous disease has progressed in severity during the study. The incidence rate is calculated by dividing the incidence by the average follow up period of 13.38 years. Results on incidence are based on findings from the clinical examination and photographs of participants in the follow up study as discussed in Chapter 5. C1 telangiectases and reticular veins are not considered when calculating incidence. The leg assigned the highest CEAP class or Basle grade of severity was used for each participant.

7.3.1 Incidence of C2 varicose veins and C3-C6 CVI

Table 7.7 presents the incidence of C2 varicose veins at follow up. At baseline, 555 participants were free of C2 varices. At follow up, 101 of these participants had developed new cases of C2 varicose veins, resulting in an incidence of 18.2% (95% CI 15.2-21.6). The annual incidence rate was 1.4% (95% CI 1.1-1.7). The majority of affected subjects (87%) had mild varicose veins. The incidence of mild (grade 1), moderate (grade 2) and severe (grade 3) C2 varicose veins was 15.7% (95% CI 12.9-18.9), 2.3% (95% CI 1.4-4.0) and 0.2% (95% CI 0.1-1.0) respectively. The annual incidence rates of mild, moderate and severe C2 varices were 1.17% (95% CI 0.95-1.44), 0.17% (95% CI 0.1-0.3) and 0.01% (95% CI 0-0.08) respectively. Of the 555 participants free from C2 varices at baseline, only 2 had varicose vein surgery during the follow up period. However, both of these participants had C2 varicose veins at follow up and therefore were correctly included as incident cases.

Of 880 participants examined at follow up, 546 had no C2 varicose veins nor C3-C6 CVI at baseline. The most common CVI condition was C3 corona phlebectatica, which had an incidence of 5.3% (95% CI 3.7-7.5) over the 13 year follow up period and an annual incidence rate of 0.40% (95% CI 0.28-0.57) [Table 7.7]. New cases of C3 oedema, C4a pigmentation, C4a eczema and C4b lipodermatosclerosis were found in 2.6% (95% CI 1.5-4.3), 2.2% (95% CI 1.3-3.8), 1.8% (95% CI 1.0-3.3) and 1.1% (95% CI 0.5-2.4) of the follow up participants respectively. Only one participant developed C4b atrophie blanche at follow up (0.2%, 95% CI 0.1-1.0). The incidence of C5 healed ulceration was 0.5% (95% CI 0.2-1.6) and C6 active ulceration was 0.2% (95% CI 0.1-1.0). Of the 546 participants with no signs of C2-C6 disease at baseline, 2 had subsequent treatment during the follow up period. However, both of these participants had C3-C6 CVI at follow up and thus were identified as incident cases of CVI.

Analysis was completed to determine the incidence of C2 varicose veins alone, C3-C6 CVI alone and both conditions together. The respective incidences were 13.9% (95% CI 11.0-17.3), 5.2% (95% CI 3.6-7.5) and 3.8% (95% CI 2.4-5.8). When analysed by severity, the majority of participants with C2 veins only had mild varices (91%), 8% were moderate and 1% was severe. In those with isolated CVI, 62% were classed as C3, 34% were C4 and 3% were C5. Of those participants with both conditions at follow up, 67% had mild varices combined with C3 CVI in 33%, C4 CVI in 24% and C5 CVI in 10%, while 33% had moderate varices combined with C3 in 57% and C4 in 43%.

7.3.2 Incidence of C2 varicose veins and C3-C6 CVI by age

The incidence of C2 varices increased significantly in a linear fashion, from 9.8% (95% CI 5.9-15.8) in those aged 18-34 years at baseline to 25.7% (95% CI 18.5-34.4) in those aged 55-64 years (p trend<0.001) [Table 7.8]. The incidence appeared to increase with age more consistently in women than in men. In women the incidence increased with every baseline age group (p trend<0.001) so that the incidence in those aged over 55 years was three times higher than in those aged 18-34 years. On the other hand, in men the rate increased with age but was lower in those aged ≥55 years, so that overall the trend was not statistically significant (P trend=0.23). It is important to note that the confidence intervals around the incidences in men aged 45-54 years and ≥55 years overlap considerably, indicating that the true incidence of C2 in these age groups may be similar.

The incidence of C3-C6 CVI increased significantly with age, from 2.1% (95% CI 0.7-6.0) in those aged less than 35 years to 17.1% (95% CI 11.2-25.2) in those aged over 55 years at baseline (p trend<0.001) [Table 7.9]. When analysed by sex, the incidence remained significantly associated with age for both males and females (p trend=0.003 and p trend=0.001 respectively). Similar to the findings on the incidence of varicose veins, male participants aged over 55 years at baseline appeared to have a lower incidence of CVI at follow up than those aged 45-54 years. However the overlap in the confidence intervals suggests that the true incidence of CVI may not be significantly different in these two age groups. Female participants aged 35-44 years had a lower incidence than those aged 18-34 year but with only 5 cases of CVI in these two age groups, the sample is too small to estimate the precise incidence of CVI.

7.3.3 Incidence of C2 varicose veins and C3-C6 CVI by sex

The incidence of C2 varicose veins and C3-C6 CVI by sex is presented in Table 7.10. The total incidence of C2 varicose veins was slightly higher in women (18.6%, 95% CI 14.8-23.1) than in men (17.6%, 95% CI 13.2-23.2) but this difference was not statistically significant (p=0.97). After adjusting for age, the incidence was 15.2% (95% CI 10.4-20.0) in men and 17.4% (95% CI 13.1-21.7%) in women (p=0.97). When C2 varicose veins were examined by severity, no difference between sexes was found (all p≥0.5). The incidence of all CVI was 10.7% (95% CI 7.2-15.5) in men compared to 8.1% (95% CI 5.7-11.6) in women (p=0.32). For each CEAP class of CVI, the incidence was higher in men but this did not reach statistical significance (all p≥0.5). The incidence of C2 varices alone, CVI alone and both conditions together was 12.1% (95% CI 8.1-17.5), 5.1% (95% CI 2.7-8.9) and 5.6% (95% CI 3.0-9.5) respectively in men and 16.4% (95% CI 11.3-19.8), 5.4% (95% CI 3.3-8.4) and 2.7% (95% CI 1.3-5.0) respectively in women.

7.3.4 Incidence of C2 varicose veins and C3-C6 CVI by leg

Of the 101 new cases of C2 varicose veins, 71 were in one leg only (70.3%) and 30 were bilateral (29.7%). The incidence of unilateral and bilateral C2 varicose veins was 12.8% (95% CI 10.3-15.8) and 5.4% (95% CI 3.8-7.6) respectively. As shown in Table 7.11, the incidence of C2 varicose veins was similar in the right and left legs (p=0.57) and remained so when analysed by severity. When men and women were compared, the incidence of C2 varicose was similar between sexes for the right and left legs (p=0.94 and p=0.97 respectively)

The incidence of unilateral and bilateral C3-C6 CVI at follow up was 2.6% (95% CI 1.5-4.3) and 6.6% (95% CI 4.8-9.0) respectively. Of the 50 new cases of CVI, 14 were in one leg only (28.0%) and 36 were in both legs (72.0%). The incidence of C3-C6 CVI did not differ by leg and this remained true when CVI was analysed by CEAP class (p>0.05) and by gender. Of the male participants, 7.9% (95% CI 5.0-12.3) had C3-C6 CVI in their right leg at follow up compared to 6.6% (95% CI 4.4-9.9) of women (p=0.29). For the left leg, 8.8% (95% CI 5.7-13.4) of men compared to 8.2% (95% CI 5.7-11.6) of women had C3-C6 CVI at the follow up examination (p=0.68).

7.3.5 Incidence of C2 varicose veins and C3-C6 CVI by social class

Table 7.12 presents the incidence of C2 varicose veins and C3-C6 CVI by social class, determined at baseline. Incidence of C2 varicose veins was lowest in skilled manual workers (Social class IIIM), 12.9% (95% CI 6.7-23.4) and highest in unskilled workers (Social class V), 30.8% (95 % CI 12.7-57.7). However, the difference was not statistically significant (P trend = 0.95).

When the six social classes were grouped together according to non-manual (Social class I to IIIN) and manual (social class IIIM to V) occupations, the overall incidence of C2 varicose veins was similar between the two groups: 18.6% (95% 15.1-22.8) in non-manual workers and 18.4% (95% CI 12.1-27.0) in manual workers (p=0.97). The incidence of C3-C6 CVI did not differ between manual and non-manual workers: 10.1% (95% CI 5.6-17.6) and 9.0 (95% CI 6.6-12.3) respectively (p=0.75). Within manual workers, unskilled workers (social class V) in particular were most likely to develop CVI, with 16.7% (95% CI 4.7-44.8) of this group presenting with CVI at follow up.

7.4 CHAPTER SUMMARY

Almost 40% of the study population had C2 varicose veins and over 20% had C3-C6 CVI at the follow up phase of the Edinburgh Vein Study. Prevalence of CVD did not differ by sex. The prevalence of all CEAP classes of CVD increased with age. There was no significant association between prevalence of C2 varices or C3-C6 CVI and social class. The incidence of C2 varicose veins was 18.2% over the 13 year follow up period. Therefore, approximately 1.4% of the study population initially free of varicose veins at baseline, developed new C2 varices each year. C3-C6 CVI had an overall incidence of 9.2% and an annual incidence rate of 0.7% per year. There was no significant gender difference for the incidence of either varicose veins or CVI. However, the incidence of both conditions did increase with age. The development of C2 varices and C3-C6 CVI was similar in the right and left legs and was not associated with social class.

TABLE 7.1 PREVALENCE OF C1-C6 CHRONIC VENOUS DISEASE IN 880 PARTICIPANTS AT BASELINE AND FOLLOW UP OF THE EDINBURGH VEIN STUDY

	BASELINE		FOLLOW UP		P VALUE *
CEAP [a]	% (95% CI)	n	% (95% CI)	n	
C1 TELANGIECTASES [b]	92.2 (90.2-93.8)	811	85.2 (82.7-87.4)	750	<0.001
Grade 1	84.1 (81.5-86.4)	740	63.9 (60.6-60.7)	562	<0.001
Grade 2	7.7 (6.1-9.7)	68	17.8 (15.5-20.5)	157	<0.001
Grade 3	0.3 (0.1-1.0)	3	3.5 (2.5-5.0)	31	<0.001
C1 RETICULAR VEINS [b]	90.2 (88.1-92.0)	794	70.1 (67.0-73.1)	617	<0.001
Grade 1	84.8 (82.3-87.0)	746	42.8 (39.6-46.1)	377	<0.001
Grade 2	5.5 (4.1-7.2)	48	21.3 (18.7-24.1)	187	<0.001
Grade 3	0 (0)	0	6.0 (4.6-7.8)	53	<0.001
C2 VARICOSE VEINS [b]	36.9 (33.8-40.2)	325	39.2 (36.0-42.5)	345	<0.001
Grade 1	30.8 (27.8-33.9)	271	21.8 (19.2-24.7)	192	<0.001
Grade 2	5.8 (4.4-7.5)	51	11.1 (9.2-13.4)	98	<0.001
Grade 3	0.3 (0.1-1.0)	3	6.3 (4.8-8.1)	55	<0.001
C3 CVI					
Corona	5.9 (4.5-7.7)	52	16.7 (14.4-19.3)	147	<0.001
Oedema	11.6 (9.6-13.9)	102	4.4 (3.3-6.0)	39	<0.001
C4 CVI					
Pigmentation	1.3 (0.7-2.2)	11	5.5 (4.1-7.2)	48	0.38
Eczema	0.2 (0.1-0.8)	2	2.2 (1.4-3.3)	19	0.41
Lipodermatosclerosis	0 (0)	0	1.8 (1.1-2.9)	16	0.24
Atrophie blanche	0 (0)	0	0.6 (0.2-1.3)	5	0.27
C5-C6 CVI					
Healed ulcer	0.5 (0.2-1.2)	4	0.8 (0.4-1.6)	7	<0.001
Active ulcer	0 (0)	0	0.1 (0.1-0.6)	1	0.30

[a] CEAP = CEAP classification of chronic venous disease (Eklof 2004)
% (95% CI) = % (95% confidence interval) in each group with CEAP class of disease at follow up
n = number in each group with CEAP class of disease at follow up.
* P value based on Chi squared test for association between prevalence at baseline and follow up
[b] Grade based on Basle classification for severity: 1 (mild), 2 (moderate) and 3 (severe)
Leg assigned the highest CEAP class or Basle grade of severity used for each participant.
* P value = chi square test for difference in prevalence of condition between baseline and follow up

TABLE 7.2 PREVALENCE OF C2 VARICOSE VEINS BY AGE AND SEX, IN 880 PARTICIPANTS OF THE FOLLOW UP PHASE OF THE EDINBURGH VEIN STUDY

AGE AT FOLLOW UP	MEN (N=390)		WOMEN (N=490)		TOTAL (N=880)	
(YEARS)	% (95% CI)	n (N)	% (95% CI)	n (N)	% (95% CI)	n (N)
25-34	0 (0)	0 (3)	18.2 (5.1-47.7)	2 (12)	14.3 (4.0-40.0)	2 (15)
35-44	15.4 (7.3-29.7)	6 (39)	17.2 (9.6-28.9)	10 (58)	16.5 (10.4-25.1)	16 (97)
45-54	38.3 (28.4-49.2)	31 (81)	22.9 (15.2-33.0)	19 (83)	30.5 (24.0-37.9)	50 (164)
55-64	40.9 (32.3-50.0)	47 (115)	38.9 (31.5-46.9)	58 (149)	39.8 (34.1-45.8)	105 (264)
≥ 65	47.4 (39.6-55.3)	72 (152)	53.2 (46.1-60.2)	100 (188)	50.6 (45.3-55.9)	172 (340)
P VALUE*	<0.001		<0.001		<0.001	

% (95% CI) = % (95% confidence interval) in each group with C2 varicose veins at follow up
n = number in each group with C2 varicose veins at follow up.
N = number in each age group at follow up.
Leg assigned the highest CEAP class or Basle grade for severity used for each participant
* P value = chi square test for linear trend for association between prevalence of C2 varicose veins and age

TABLE 7.3 PREVALENCE OF C3-C6 CHRONIC VENOUS INSUFFICIENCY (CVI) BY AGE AND SEX, IN 880 PARTICIPANTS AT THE FOLLOW UP PHASE OF THE EDINBURGH VEIN STUDY

AGE AT BASELINE	MEN (N=390)		WOMEN (N=490)		TOTAL (N=880)	
(YEARS)	% (95% CI)	n (N)	% (95% CI)	n (N)	% (95% CI)	n (N)
25-34	0	0 (3)	9.1 (1.6-37.7)	1 (12)	7.1 (1.3-31.5)	1 (15)
35-44	2.6 (0.5-13.2)	1 (38)	3.4 (0.9-11.7)	2 (58)	3.1 (1.1-8.7)	3 (97)
45-54	12.3 (6.9-21.3)	10 (81)	10.8 (5.8-19.3)	9 (83)	11.6 (7.5-17.4)	19 (164)
55-64	20.0 (13.7-28.2)	23 (115)	16.1 (11.1-22.8)	24 (149)	17.8 (13.7-22.9)	47 (264)
≥ 65	36.8 (29.6-44.8)	56 (152)	29.3 (23.2-36.1)	55 (188)	32.6 (27.9-37.8)	111 (340)
P VALUE*	<0.001		<0.001		<0.001	

% (95% CI) = % (95% confidence interval) in each group with C3-C6 CVI at follow up
n = number in each group with C3-C6 CVI at follow up.
N = number in each age group at follow up.
Leg assigned the highest CEAP class or Basle grade for severity used for each participant
CVI includes C3, C4, C5 and C6, with the limb assigned the highest value used for each participant.
* P value = chi square for linear trend for association between prevalence of C3-C6 CVI and age

TABLE 7.4 PREVALENCE OF C1-C6 CHRONIC VENOUS DISEASE IN MEN AND WOMEN AT THE FOLLOW UP PHASE OF THE EDINBURGH VEIN STUDY

	MEN (N=390)		WOMEN (N=490)		P VALUE*
CEAP [a]	**% (95% CI)**	**N**	**% (95% CI)**	**N**	
C1 TELANGIECTASES [b]	79.0 (74.7-82.7)	308	90.2 (87.3-92.5)	442	<0.001
Grade 1	65.9 (61.1-70.4)	257	62.2 (57.9-66.4)	305	0.001
Grade 2	11.0 (8.3-14.5)	43	23.3 (19.7-27.2)	114	<0.001
Grade 3	2.1 (1.0-4.0)	8	4.7 (3.2-6.9)	2	<0.001
C1 RETICULAR VEINS [b]	67.2 (62.4-71.7)	262	72.4 (68.3-76.2)	355	0.11
Grade 1	44.1 (39.3-49.1)	172	41.8 (37.6-46.2)	205	0.50
Grade 2	17.7 (14.2-21.8)	69	24.1 (20.5-28.1)	118	0.02
Grade 3	5.4 (3.6-8.1)	21	6.5 (4.7-10.0)	32	0.2
C2 VARICOSE VEINS [b]	40.0 (35.3-44.5)	156	38.6 (34.4-42.9)	189	0.67
Grade 1	21.8 (18.0-26.2)	185	21.8 (18.4-25.7)	107	0.97
Grade 2	11.5 (8.7-15.1)	45	10.8 (8.4-13.9)	53	0.77
Grade 3	6.7 (4.6-9.6)	26	5.9 (4.2-8.4)	29	0.72
C3 CVI					
Corona	18.7 (15.2-22.9)	73	15.1 (12.2-18.5)	74	0.18
Oedema	4.9 (3.1-7.5)	19	4.1 (2.7-6.2)	20	0.69
C4 CVI					
Pigmentation	7.2 (5.0-10.2)	28	4.1 (2.7-6.2)	20	0.06
Venous eczema	1.5 (0.7-3.3)	6	2.7 (1.6-4.5)	13	0.37
Lipodermatosclerosis	1.3 (0.6-3.0)	5	2.2 (1.3-4.0)	11	0.42
Atrophie blanche	0.5 (0.1-1.8)	2	0.6 (0.2-1.8)	3	0.61
C5-C6 CVI					
Healed ulcer	0.8 (0.2-2.2)	3	0.8 (0.3-2.1)	4	0.62
Active ulcer	0.2 (0.1-0.4)	1	0 (0)	0	0.44

[a] CEAP = CEAP classification of chronic venous disease (Eklof 2004)
% (95% CI) = % (95% confidence interval) in each group with class of disease at follow up
N = number in each group with class of disease at follow up
Leg assigned the highest CEAP class or Basle grade for severity used for each participant
[b] Grade based on Basle classification for severity: 1 (mild), 2 (moderate) and 3 (severe)
* P value = chi square test for difference in prevalence of condition between men and women

TABLE 7.5 PREVALENCE OF C2 VARICOSE VEINS AND C3-C6 CVI (BY SEVERITY) IN THE RIGHT AND LEFT LEGS AT THE FOLLOW UP PHASE OF THE EDINBURGH VEIN STUDY

CEAP [a]	RIGHT LEG		LEFT LEG		P VALUE*
	% (95% CI)	(N)	% (95% CI)	(N)	
C2 VARICOSE VEINS [b]	28.7 (25.9-31.8)	253	29.6 (26.7-32.8)	261	<0.001
Grade 1	15.8 (13.5-18.3)	139	18.3 (15.9-21.0)	161	<0.001
Grade 2	9.0 (7.3-11.1)	79	6.9 (5.4-8.8)	61	<0.001
Grade 3	4.0 (2.9-5.5)	35	4.4 (3.3-6.0)	39	0.57
C3-C6 CVI	16.7 (14.4-19.3)	147	17.6 (15.2-20.3)	155	<0.001
C3 CVI [c]	10.9 (9.0-13.1)	96	11.8 (9.7-14.0)	104	<0.001
C4 CVI [d]	5.2 (3.9-6.9)	46	5.6 (4.2-7.3)	49	0.74
C5-C6 CVI [e]	0.6 (0.2-1.3)	5	0.2 (0.1-0.8)	2	0.67

[a] CEAP = CEAP classification of chronic venous disease (Eklof 2004)
% (95% CI) = % (95% confidence interval) in each group with C2 varicose veins/ CVI at follow up
N = number in each group with C2 varicose veins/ CVI at follow up.
Leg assigned the highest CEAP class or Basle grade for severity used for each participant
[b] Grade based on Basle classification for severity: 1 (mild), 2 (moderate) and 3 (severe)
[c] C3 = corona phlebectatica and venous oedema
[d] C4 = C4a pigmentation, C4a venous oedema, C4b lipodermatosclerosis and C4b atrophie blanche
[e] C5-C6 = C5 healed and C6 active venous ulceration
* P value = chi square test for difference in incidence of C2 varices or C3-C6 CVI by leg

TABLE 7.6 PREVALENCE OF C2 VARICOSE VEINS AND C3-C6 CHRONIC VENOUS INSUFFICIENCY (CVI) AT THE FOLLOW UP PHASE, DETERMINED BY SOCIAL CLASS AT THE BASELINE PHASE OF THE EDINBURGH VEIN STUDY

	C2 VARICOSE VEINS*		C3-C6 CVI	
SOCIAL CLASS [a]	**% (95% CI)**	**n (N)**	**% (95% CI)**	**n (N)**
I	33.3 (24.2-43.9)	28 (84)	16.7 (10.2-26.1)	14 (84)
II	39.4 (34.3-44.7)	132 (335)	22.1 (18.0-26.8)	74 (335)
IIIN	38.1 (31.5-45.2)	72 (189)	21.2 (15.9-27.5)	40 (189)
IIIM	36.6 (27.9-46.4)	37 (101)	18.8 (12.4-27.5)	19 (101)
IV	47.8 (34.1-61.9)	22 (46)	23.9 (13.9-37.9)	11 (46)
V	51.9 (34.0-69.3)	14 (27)	18.5 (8.2-36.7)	5 (27)

*C2 varicose veins include all Basle grades for severity: 1 (mild), 2 (moderate) and 3 (severe).
CVI includes all CEAP classes: C3, C4, C5 and C6.
% (95% CI) = % (95% confidence interval) in each group with C2 varicose veins or C3-C6 CVI at follow up
n = number in each group with C2 varicose veins or C3-C6 CVI at follow up
(N) = number in each social class group at baseline
[a] Social class based on occupation at baseline. I: professional, II: managerial/technical, IIIN: skilled (non-manual), IIIM: skilled (manual), IV: partly skilled, V: unskilled, VI: other
Based on a total = 782. Excluded are housewives (75), students (20), members of armed forces (2), missing (1)

TABLE 7.7 13 YEAR INCIDENCE OF C2 VARICOSE VEINS AND C3-C6 CVI AT FOLLOW UP IN PARTICIPANTS FREE OF DISEASE AT THE BASELINE PHASE OF THE EDINBURGH VEIN STUDY

	INCIDENCE		ANNUAL INCIDENCE RATE
CEAP [a]	% (95% CI)	N	% (95% CI)
C2 VARICOSE VEINS [b]	18.2 (15.2-21.6)	101	1.36 (1.12-1.65)
Grade 1	15.7 (12.9-18.9)	87	1.17 (0.95-1.44)
Grade 2	2.3 (1.4-4.0)	13	0.17 (0.10-0.30)
Grade 3	0.2 (0.1-1.0)	1	0.02 (0.00-0.08)
C3 CVI			
Corona	5.3 (3.7-7.5)	29	0.40 (0.28-0.57)
Oedema	2.6 (1.5-4.3)	14	0.19 (0.11-0.32)
C4 CVI			
C4a Pigmentation	2.2 (1.3-3.8)	12	0.16 (0.09-0.29)
C4a Eczema	1.8 (1.0-3.3)	10	0.13 (0.07-0.25)
C4b Lipodermatosclerosis	1.1 (0.5-2.4)	6	0.08 (0.04-0.18)
C4b Atrophie blanche	0.2 (0.1-1.0)	1	0.02 (0.00-0.08)
C5-C6 CVI			
C5 Healed ulcer	0.5 (0.2-1.6)	3	0.04 (0.01-0.12)
C6 Active ulcer	0.2 (0.1-1.0)	1	0.02 (0.00-0.08)

[a] CEAP = CEAP classification of chronic venous disease (Eklof 2004)
% (95% CI) = % (95% confidence interval) in each group with C2 varicose veins/ CVI at follow up
N = number in each group with C2 varicose veins/ CVI at follow up.
Leg assigned the highest CEAP class or Basle grade for severity used for each participant
[b] Grade based on Basle classification for severity: 1 (mild), 2 (moderate) and 3 (severe)
Incidence of C2 varicose veins based on the number of new cases of C2 varicose veins at follow up divided by the number of participants free from C2 varicose veins at baseline.
Incidence of C3-C6 CVI based on the number of new cases of C3-C6 CVI at follow up, divided by the number of participants free from C2 varices and C3-C6 CVI at baseline.
Participants with C2 varicose veins at baseline and C3-C6 CVI at follow up are not counted as incident cases of C3-C6 CVI as they are cases where existing venous disease has progressed rather than cases where new venous disease has developed.

TABLE 7.8 13 YEAR INCIDENCE OF C2 VARICOSE VEINS AT FOLLOW UP BY AGE AND SEX, IN 555 MEN AND WOMEN WITH NO C2 VARICOSE VEINS AT THE BASELINE PHASE OF THE EDINBURGH VEIN STUDY

AGE AT BASELINE	MEN (N=221)		WOMEN (N=334)		TOTAL (N=555)	
(YEARS)	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N
18-34	10.0 (4.4-21.4)	5	9.7 (5.2-17.4)	9	9.8 (5.9-15.8)	14
35-44	18.2 (10.2-30.3)	10	15.4 (9.0-25.5)	12	16.5 (11.2-23.8)	22
45-54	22.9 (14.6-33.9)	16	20.9 (13.9-30.0)	20	21.7 (16.1-28.6)	36
≥ 55	17.4 (9.1-30.7)	8	31.4 (21.5-43.2)	21	25.7 (18.5-34.4)	29
P VALUE *	0.23		<0.001		<0.001	

% (95% CI) = % (95% confidence interval) in each group with C2 varicose veins at follow up
N = number in each group with C2 varicose veins at follow up
C2 varicose veins includes all Basle grades for severity: 1 (mild), 2 (moderate) and 3 (severe)
Leg assigned the highest CEAP class or Basle grade for severity used for each participant
* P value = chi square linear test for trend for association of incidence of C2 varicose veins with age
Incidence of C2 varicose veins based on the number of new cases of C2 varicose veins at follow up divided by the number of participants free from C2 varicose veins at baseline.

TABLE 7.9 13 YEAR INCIDENCE OF C3-C6 CHRONIC VENOUS INSUFFICIENCY AT FOLLOW UP BY AGE AND SEX, IN 546 PARTICIPANTS WITH NO CLINICAL SIGNS OF C2 VARICOSE VEINS OR C3-C6 CVI AT THE BASELINE PHASE OF THE EDINBURGH VEIN STUDY

AGE AT BASELINE	MEN (N=215)		WOMEN (N=331)		TOTAL (N=546)	
(YEARS)	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N
18-34	0 (0)	0	3.3 (1.1-9.2)	3	2.1 (0.7-6.0)	3
35-44	7.3 (2.9-17.2)	4	2.6 (0.7-9.0)	2	4.5 (2.1-9.6)	6
45-54	19.7 (11.9-30.8)	13	9.5 (5.1-17.0)	9	13.7 (9.2-19.8)	22
≥ 55	13.6 (6.4-26.7)	6	19.4 (11.7-30.4)	13	17.1 (11.2-25.2)	19
P VALUE *	0.003		0.001		<0.001	

% (95% CI) = % (95% confidence interval) in each group with C3-C6 CVI at follow up
N = number in each group with C3-C6 CVI at follow up
Leg assigned the highest CEAP class or Basle grade for severity used for each participant
* P value = chi square linear test for trend for association of incidence of C3-C6 CVI with age
Incidence of C3-C6 CVI based on the number of new cases of C3-C6 CVI at follow up, divided by the number of participants free from C2 varices and C3-C6 CVI at baseline.
Participants with C2 varicose veins at baseline and C3-C6 CVI at follow up are not counted as incident cases of C3-C6 CVI as they are cases where existing venous disease has progressed rather than cases where new venous disease has developed.

TABLE 7.10 13 YEAR INCIDENCE OF C2 VARICOSE VEINS AND C3-C6 CHRONIC VENOUS INSUFFICIENCY AT FOLLOW UP, IN MEN AND WOMEN FREE OF CHRONIC VENOUS DISEASE AT THE BASELINE PHASE OF THE EDINBURGH VEIN STUDY

	MEN		WOMEN		TOTAL		P VALUE *
CEAP [a]	% (95% CI)	(N)	% (95% CI)	(N)	% (95% CI)	(N)	
C2 VARICOSE VEINS [b]	17.6 (13.2-23.2)	39	18.6 (14.8-23.1)	62	18.2 (15.2-21.6)	101	0.78
Grade 1	14.9 (10.8-20.2)	33	16.2 (12.6-20.5)	54	15.7 (12.9-18.9)	87	0.13
Grade 2	2.3 (0.9-5.2)	5	2.4 (1.2-4.6)	8	2.3 (1.4-4.0)	13	0.83
Grade 3	0.5 (0.9-2.5)	1	0 (0)	0	0.2 (0.1-1.0)	1	0.26
C3-C6 CVI	10.7 (7.2-15.5)	23	8.2 (5.7-11.6)	27	9.2 (7.0-11.9)	50	0.32
C3 [c]	6.0 (3.6-10.1)	13	4.8 (3.0-7.7)	16	5.3 (3.7-7.5)	29	0.65
C4 [d]	3.7 (1.9-7.2)	8	3.0 (1.7-5.5)	10	3.3 (2.1-5.2)	18	0.78
C5-C6 [e]	0.9 (0.3-3.3)	2	0.3 (0.6-1.7)	1	0.6 (0.2-1.6)	3	0.33

[a] CEAP = CEAP classification of chronic venous disease (Eklof 2004)
% (95% CI) = % (95% confidence interval) in each group with C2 varicose veins/ C3-C6 CVI at follow up
(N) = number in each group with C2 varicose veins/ C3-C6 CVI at follow up.
Leg assigned the highest CEAP class or Basle grade for severity used for each participant
[b] Grade based on Basle classification for severity: 1(mild), 2 (moderate) and 3 (severe). Measured in men (n=221), women (n=334)
[c] C3 = corona phlebectatica and venous oedema. Measured in men (n=215), women (n=331)
[d] C4 = C4a pigmentation, C4a venous oedema, C4b lipodermatosclerosis and C4b atrophie blanche. Measured in men (n=215), women (n=331)
[e] C5-C6 = C5 healed and C6 active venous ulceration. Measured in men (n=215), women (n=331)
*P value = chi square test for the difference in incidence of C2 varicose veins or C3-C6 CVI between men and women

TABLE 7.11 13 YEAR INCIDENCE OF C2 VARICOSE VEINS AND C3-C6 CVI (BY GRADE) IN THE RIGHT AND LEFT LEGS AT THE FOLLOW UP PHASE OF THE EDINBURGH VEIN STUDY

	RIGHT LEG		LEFT LEG		P VALUE*
CEAP [a]	% (95% CI)	(N)	% (95% CI)	(N)	
C2 VARICOSE VEINS [b]	11.9 (9.5-14.9)	66	11.7 (9.3-14.7)	65	<0.001
Grade 1	9.7 (7.5-12.5)	54	9.9 (7.7-12.7)	55	
Grade 2	1.9 (1.1-3.5)	11	1.6 (0.9-3.1)	9	
Grade 3	0.2 (0.1-1.0)	1	0.2 (0.1-1.0)	1	
C3-C6 CVI	7.1 (5.3-9.6)	39	8.4 (6.4-11.1)	46	<0.001
C3 [c]	3.8 (2.5-5.8)	21	4.9 (3.4-7.1)	27	
C4 [d]	2.9 (1.8-4.7)	16	3.3 (2.1-5.2)	18	
C5-C6 [e]	0.4 (0.1-1.3)	2	0.2 (0.1-1.0)	1	

[a] CEAP = CEAP classification of chronic venous disease (Eklof 2004)
% (95% CI) = % (95% confidence interval) in each group with C2 varicose veins/ C3-C6 CVI at follow up
(N) = number in each group with C2 varicose veins/ C3-C6 CVI at follow up.
Leg assigned the highest CEAP class or Basle grade for severity used for each participant
[b] Grade based on Basle classification for severity: 1 (mild), 2 (moderate) and 3 (severe). Measured in men (n=215), women (n=331)
[c] C3 = corona phlebectatica and venous oedema.
[d] C4 = C4a pigmentation, C4a venous oedema, C4b lipodermatosclerosis and C4b atrophie blanche.
[e] C5-C6 = C5 healed and C6 active venous ulceration.
*P value = chi square test for the difference in incidence of C2 varicose veins or C3-C6 CVI between legs

TABLE 7.12 13 YEAR INCIDENCE OF C2 VARICOSE VEINS AND C3-C6 CHRONIC VENOUS INSUFFICIENCY (CVI) AT FOLLOW UP, DETERMINED BY SOCIAL CLASS IN PARTICIPANTS WITH NO C2 VARICOSE VEINS OR C3-C6 CVI AT THE BASELINE PHASE OF THE EDINBURGH VEIN STUDY

	C2 VARICOSE VEINS (N=555)		C3-C6 CVI (N=546)	
SOCIAL CLASS *	**% (95% CI)**	**N**	**% (95% CI)**	**N**
I	23.7 (14.7-36.0)	14	8.5 (3.7-18.4)	5
II	18.3 (13.6-24.1)	38	9.3 (6.0-14.1)	19
IIIN	16.8 (11.3-24.3)	21	8.9 (5.0-15.2)	11
IIIM	12.9 (6.7-23.4)	8	9.8 (4.6-19.8)	6
IV	25.0 (12.7-43.4)	7	7.7 (2.1-24.1)	2
V	30.8 (12.7-57.4)	4	16.7 (4.7-44.8)	2

C2 varicose veins includes all Basle grades: 1 (mild), 2 (moderate) and 3 (severe)
% (95% CI) = % in each group with C2 varicose veins or C3-C6 CVI at follow up (95% confidence interval)
N = number in each group with C2 varicose veins or C3-C6 CVI at follow up
* Social class based on occupation at baseline. I: professional, II: managerial/technical, IIIN: skilled (non-manual), IIIM: skilled (manual), IV: partly skilled, V: unskilled, VI: other
Incidence of C2 varicose veins by social class based on a total of 495 participants and incidence of C3-C6 CVI by social class based on a total of 486 participants. Excluded = housewives (44), students (14), and members of armed forces (2)
Incidence of C2 varicose veins based on the number of new cases of C2 varicose veins at follow up divided by the number of participants free from C2 varicose veins at baseline.
Incidence of C3-C6 CVI based on the number of new cases of C3-C6 CVI at follow up, divided by the number of participants free from C2 varices and C3-C6 CVI at baseline.
Participants with C2 varicose veins at baseline and C3-C6 CVI at follow up are not counted as incident cases of C3-C6 CVI as they are cases where existing venous disease has progressed rather than cases where new venous disease has developed.

CHAPTER 8: PREVALENCE AND INCIDENCE OF VENOUS REFLUX

8.1 CHAPTER OUTLINE

Duplex ultrasound scanning is considered to be the gold standard for assessment of venous reflux as it evaluates anatomical and functional haemodynamics to quantify reflux in deep and superficial veins (Labropoulos 2005). This chapter presents reflux data on the Edinburgh Vein Study follow up participants. The prevalence of reflux by vein segment, venous system, age and sex at both the baseline and follow up phases of the study will be presented. The incidence of venous reflux at follow up by vein segment, venous system, age and sex will then be measured.

8.2 ASSESSMENT OF VENOUS REFLUX

The assessment of venous reflux was discussed in Chapter 4. Two measures of reflux were made in each vein segment, with the mean used in the final reflux measure. For all vein segments, if there was no blood flowing through the vein or the segment could not be visualised or correctly identified, it was recorded as a missing value rather than assuming there was no reflux present in the segment.

Data on reflux is presented by vein segment and also by venous system. Venous system reflux is categorised into three groups: (1) deep reflux only, (2) superficial reflux only and (3) combined deep and superficial reflux. Deep reflux only is defined as reflux ≥ 0.5 seconds in one or more deep vein segments but not in any superficial segments. Superficial reflux only is defined as reflux ≥ 0.5 seconds in one or more superficial vein segments but not in any deep segments. Combined deep and superficial reflux is defined as reflux ≥ 0.5 seconds in one or more deep segments and reflux ≥ 0.5 seconds in one or more superficial segments. In determining reflux by system, if one deep segment was missing, deep system reflux is classified as present if one or more other deep segments had reflux. If all other deep segments had no reflux, then the deep system reflux is classified as missing. The same was true for superficial system reflux. Combined deep and superficial reflux is assigned if one or more deep and superficial segments had reflux in either leg. Where reflux measurements for both deep and superficial segments were missing and all other segments had no reflux, combined reflux is classified as missing.

8.3 PREVALENCE OF VENOUS REFLUX AT BASELINE

Of the 880 participants who took part in both stages of the study, reflux status at baseline was successfully determined in 759 participants. Reflux could not be measured in 121 participants. Two scans were abandoned, 4 examinations were performed at home, in 4 patients there was no blood flow in the vein and in 111 participants the vein could not be imaged. Of the 759 participants with valid reflux measurements, 443 had some evidence of reflux at baseline (58.4%).

8.3.1 Prevalence of venous reflux by vein segment

Table 8.1 displays the prevalence of venous reflux ≥ 0.5 seconds for individual vein segments in the right, left, and both legs together, at the baseline phase of the study. There was no significant difference in the prevalence of reflux in any individual vein segment between the right and left legs (all p≥0.05). The GSV in the lower third of the thigh was the most common site of reflux, with a prevalence of 17.9% (95% CI 15.1-21.0) in the right leg, 16.8% (95% CI 14.2-19.8) in the left leg and 6.9% (95% CI 5.2-8.9) in both legs. Within the superficial system, the prevalence of reflux was lowest in the SSV. For deep vein segments the POP vein above the knee crease had the highest prevalence of reflux, 12.6% (95% CI 10.4-15.1) in the right leg, 11.9% (95% CI 9.8-14.3) in the left leg and 4.2% (95% CI 3.0-5.8) in both legs. Reflux was least common in the FV origin, with a prevalence of 6.0% (95% CI 4.5-7.8), 4.8% (95% CI 3.5-6.4) and 1.7% (95% CI 1.0-2.8) in the right, left and both legs respectively.

8.3.2 Prevalence of venous reflux by venous system

Of the 759 participants with a complete set of reflux measurements at baseline, 41.6% (n=319) had no reflux. The prevalences of deep reflux only, superficial reflux only and combined reflux at baseline were 22.2% (95% CI 19.0-25.7), 16.3% (95% CI 13.6-19.4) and 19.9% (95% CI 16.9-23.2) respectively. Of those with deep reflux only, 39.9% were in the right leg, 31.5% in the left, and 28.6% in both legs. The prevalence of superficial reflux only was 37.6% in the right leg 41.6% in the left leg and 20.7% in both legs. Of the 151 participants with combined reflux at baseline, 97% had deep and superficial reflux in the same leg while only 3% had deep reflux in one leg but superficial reflux in the other leg.

8.3.3 Prevalence of venous reflux by age

The prevalence of reflux ≥ 0.5 seconds in any leg by age group at baseline is presented in Table 8.2. The prevalence of reflux increased with age in four vein segments; the CFV, FV origin, GSV origin and GSV in the lower third of thigh. Although, the number of participants aged 18-24 years with reflux in the CFV or FV origin at baseline was small, the prevalence increased significantly with age for both segments (p trend=0.003 and p trend=0.03 respectively). For the GSV, the prevalence of reflux in both the origin and in the lower third of the thigh, increased with every age group so that in participants aged 55-64 years, the prevalence was approximately three times higher than in those aged 18-24 years (both P trend<0.001).

When reflux at baseline was analysed by venous system, over half (55.3%) of participants aged 18-24 years at baseline had no reflux compared to 31.1% of participants aged 55-64 years (p trend<0.001) [Table 8.3]. The prevalence of reflux in the deep system only, increased from 16.3% (95% CI 7.1-32.2) in those aged 18-24 years to 25.4% (95% CI 18.9-33.4) in those aged 35-44 years. However, in the older age groups, the prevalence decreased so that in participants aged 55-64 years, the prevalence was lower than in those aged 18-24 years (p trend=0.047). The prevalence of reflux in the superficial system only, increased significantly with age from 10.5% (95% CI 3.3-25.4) in those aged 18-24 years to 22.6% (95% CI 16.9-29.8) in those aged 55-64 years (p trend<0.001). Age was also significantly associated with combined deep and superficial venous reflux. The prevalence increased from 14.3% (95% CI 5.8-29.7) to 26.3% (95% CI 20.2-33.6) in participants aged 18-24 years and 55-64 years respectively (p trend=0.001).

8.3.4 Prevalence of venous reflux by sex

The prevalence of reflux in individual vein segments in men and women at baseline is displayed in Figure 8.1. For all five deep vein segments assessed, the prevalence of reflux was significantly higher in men than women ($p<0.05$). For the superficial vein segments, the prevalence of reflux appeared to be slightly higher in women however this finding was not statistically significant for any segment (all $p\geq0.05$). Figure 8.2 shows the prevalence of reflux by system in men and women at baseline. Men had a significantly higher prevalence of deep reflux only (25.2%, 95% CI 20.6-30.6) compared to women (14.4%, 95% CI 11.3-18.1) ($p<0.001$). Conversely, a significantly higher proportion of women (20.3%, 95% CI 16.3-25.1) than men (11.6%, 95% CI 8.4-15.6) had superficial reflux only ($p=0.002$). The prevalence of combined deep and superficial reflux at baseline did not differ significantly between male (20.0%, 95% CI 15.8-25.0) and female study participants (16.5%, 95% CI 37.1-58.0) ($p=0.22$).

8.4 PREVALENCE OF VENOUS REFLUX AT FOLLOW UP

Of the 880 study participants, reflux status at follow up could not be determined in 30 as the scan was abandoned in 11 participants, there was no blood flow in the vein in 4 and in 15 participants the vein could not be imaged. Among the 850 participants in whom reflux status at follow up could be determined, 58.8% (n=500) participants had no reflux whilst 41.2% (n=350) had evidence of venous reflux at the follow up examination.

8.4.1 Prevalence of venous reflux by vein segment

Table 8.4 displays the prevalence of reflux ≥ 0.5 seconds at follow up, by individual vein segments in the right and left legs separately and both legs together. There were no significant differences in the prevalence of reflux in any vein segments between the right and left legs (all p≥0.05). As at baseline, the prevalence was highest in the GSV in the lower third of the thigh, with 21.6% (95% CI 18.7-24.9) of follow up participants with reflux in this segment in the right leg, 17.2% (95% CI 14.5-20.2) in the left leg and 9.6% (95% CI 7.7-11.9) in both legs. Within the superficial system, the SSV was the least affected with a prevalence of 8.4% (95% CI 6.6-10.4) in the right leg, 3.8% (95% CI 3.3-6.2) in the left leg and 1.1% (95% CI 0.5-2.0) in both legs. Within the deep system, the reflux was most common in the POP vein, particularly above the knee crease, with a prevalence of 7.2% (95% CI 5.6-9.1) in the right leg, 5.8% (95% CI 4.3-7.6) in the left leg and 2.3% (1.4-3.5) in both legs.

8.4.2 Prevalence of venous reflux by venous system

The prevalences of deep reflux only, superficial reflux only and combined reflux at follow up were 6.5% (95% CI 4.9-8.3), 23.8% (95% CI 20.7-27.3) and 11.0 (95% CI 9.0-13.5) respectively. Of those with reflux in the deep veins only, 41.8% were in the right leg. 43.6% in the left leg and 14.6% in both legs. For superficial veins, the prevalence of reflux was 38.4%, 28.2% and 33.4% in the right, left and both legs respectively. Of those with combined reflux, 97% had reflux in the deep and superficial veins of the same leg and only 3% had reflux in the deep veins in one leg and the superficial veins of the other leg.

8.4.3 Prevalence of venous reflux by age

The prevalence of venous reflux categorised by age group at follow up, is displayed in Table 8.5. When individual vein segments were analysed, prevalence in the GSV was the only vein which showed an association with age. Reflux in the origin of the GSV was prevalent in 6.7% (95% CI 0.0-3.3) of participants aged 25-34 years and increased more than five times to 34.3% (95% CI 28.3-41.2) in those aged over 65 years at follow up (p trend<0.001). Reflux in the GSV in the lower third of the thigh was also significantly associated with increased age. The prevalence of reflux rose from 13.8% (95% CI 7.7-23.0) in those aged 35-44 years and increased three fold to 44.3% (95% CI 37.6-52.0) in those aged over 65 years at follow up (p trend<0.001).

When analysed by venous system, 73.3% of participants aged 25-34 years had no reflux compared to 47.2% of those aged over 65 years at the follow up examination (p trend<0.001) [Table 8.6]. The prevalence of deep only and superficial only reflux was the same in participants aged 25-34 years (6.7%, 95% CI 0.33-32.9). However, while the prevalence of superficial reflux only increased with age (p trend<0.001), the prevalence of deep reflux only did not (p trend=0.46). Reflux confined to the superficial veins increased almost five fold, from 6.7% (95% CI 0.33-32.9) in those aged 25-34 years to 32.6% (95% CI 26.8-39.3) in those aged over 65 years at follow up (p trend<0.001). The prevalence of combined deep and superficial reflux showed no significant association with age (p trend=0.05).

8.4.4 Prevalence of venous reflux by sex

Figure 8.3 displays the prevalence of venous reflux ≥ 0.5 seconds in individual vein segments in either leg, in male and female follow up participants. For all deep veins, men had an equal or higher prevalence of venous reflux than women, but the difference did not reach statistical significance for any segment (all p≥0.05). Conversely, women had a higher prevalence of reflux in all the superficial veins, although the sex difference was not statistically significant for any segment (all p≥0.05). Prevalence of reflux by system in men and women is shown in Figure 8.4. There was no significant difference in the prevalence of reflux in the deep system only, between men (6.8%, 95% CI 4.5-9.8) and women (6.2%, 95% CI 4.3-8.8) (p=0.75). Reflux confined to the superficial veins only, was more prevalent in women (28.1%, 95% CI 23.6-33.3) than in men (18.4%, 95% CI 14.4-23.1) (p<0.001). The prevalence of combined in the deep and superficial systems, did not differ by sex (p=0.06).

8.5 INCIDENCE OF VENOUS REFLUX FROM BASELINE TO FOLLOW UP

The incidence of venous reflux at follow up is defined as the number of new cases of venous reflux ≥ 0.5s at follow up, divided by the number of participants with no reflux at baseline. To measure the incidence, participants with no venous reflux ≥ 0.5 s in any deep or superficial vein at baseline were selected. In total 306 participants had no reflux at baseline and thus formed the denominator on which the incidence calculations are based.

8.5.1 Incidence of venous reflux by vein segment

The 13 year incidence of reflux ≥ 0.5 seconds at follow up in vein segments in the right and left legs separately and together is shown in Table 8.7. The most common vein segment to develop reflux was the GSV in the lower third of the thigh. The incidence of reflux in this vein segment was 4.6% (95% CI 2.6-7.5) in the right leg, 3.9% (95% CI 2.1-6.7) in the left leg and 0.3% (95% CI 0.02-1.6) in both legs. The incidence of venous reflux in the deep system was very low. Only two participants developed reflux in the CFV (0.7%, 95% CI 0.1-2.2). One participant developed reflux in the FV in the lower thigh (0.3%, 95% CI 0.01-1.6) while there were no new cases of reflux in the FV origin at follow up. The incidence of reflux in the POP vein below the knee crease was 2.3% (95% CI 1.0-4.5) and 1.0% (95% CI 0.2-2.7) for the right and left legs respectively, whilst above the knee crease the incidence of reflux was lower still with 1.3% (95% CI 0.4-3.1) and 0.7% (95% CI 0.1-2.2) of the right and legs developing reflux at follow up.

8.5.2 Incidence of venous reflux by venous system

Of the 306 participants free of any type of reflux at baseline, 39 (12.7%) presented with new reflux at follow up. The incidences of deep reflux only, superficial reflux only and combined reflux were 2.6% (95% CI 1.2-4.9), 8.8% (95% CI 5.9-12.7) and 1.3% (95% CI 0.4-3.2) respectively. Of the 8 participants with deep reflux only, 4 were in the right leg, 3 in the left leg and 1 had deep reflux in both legs. Twenty seven participants had superficial reflux only, 14 in the right leg, 12 in the left leg and 1 in both legs. Only 4 participants had combined reflux at follow up, all of whom and deep and superficial reflux in the same leg.

8.5.3 Incidence of venous reflux by age

The incidence of reflux ≥ 0.5 seconds in any leg, by individual vein segment, venous system and age group at baseline is summarised in Table 8.8. Age was not associated with increased incidence of reflux in any individual vein segment (all p trend>0.05). When analysed by venous system, no significant association was observed between the incidence of venous reflux and age (all p trend>0.05) [Table 8.9]. It should be noted that the number of new cases of venous reflux was very small and thus the true incidence within these age groups cannot be estimated with precision.

8.5.4 Incidence of venous reflux by sex

There were no sex differences in the incidence of reflux in any leg by individual veins segment (all p>0.05). For both sexes, the highest incidence was in the GSV in the lower third of the thigh, with 6.1% (95% CI 2.8-11.5) of male and 9.6% (95% CI 5.8-15.0) of female participants developing reflux in this segment at follow up (p=0.26). The POP vein below the knee crease was the most common deep vein where reflux developed in both sexes. The incidence in this segment was 3.8% (95% CI 1.4-8.5) and 2.2% (95% CI 0.7-5.4) in men and women respectively (p=0.31). When analysed by system affected in any leg, the incidence of deep reflux only at follow up was 3.1% (95% CI 1.0-74.0) in men and 2.3% (95% CI 0.7-5.4) in women (p=0.45). The incidence of superficial reflux only was 6.1% (95% CI 2.8-11.6) in men and 10.9% (95% CI 6.7-16.6) in women (p=0.15). Combined deep and superficial reflux developed in 1.5% (95% CI 0.3-5.1) and 1.1% (95% CI 0.2-3.8) of male and female participants respectively (p=0.57). As stated previously, the size of the sample with new reflux, particularly in the deep veins, may be too low to estimate the incidence by sex with precision.

8.6 CHAPTER SUMMARY

The EVS study sample comprised 880 participants who were examined at baseline and follow up. At both stages of the study, the prevalence of reflux ≥0.5s was highest in the GSV located in in the superficial system. The prevalence of superficial reflux increased with age and was more common in women than in men. The incidence of venous reflux ≥0.5s at follow up was very low. Only 12.7% of those with no reflux at baseline developed reflux at follow up, the majority of which was in the superficial venous system. Neither age nor sex was associated with the incidence of reflux.

TABLE 8.1 PREVALENCE OF REFLUX ≥ 0.5 SECONDS DURATION IN THE RIGHT AND LEFT LEGS SEPARATELY AND IN BOTH LEGS TOGETHER AT BASELINE

	RIGHT LEG		LEFT LEG		BOTH LEGS	
REFLUX AT BASELINE	**TOTAL [a]**	**% (N)**	**TOTAL [a]**	**% (N)**	**TOTAL [b]**	**% (N)**
DEEP SYSTEM						
CFV	874	8.4 (73)	874	8.4 (73)	874	2.6 (23)
FV origin	873	6.0 (52)	874	4.8 (42)	873	1.7 (15)
FV lower thigh	873	6.6 (58)	873	6.8 (59)	873	2.1 (18)
POP above knee crease	874	12.6 (110)	874	11.9 (104)	874	4.2 (37)
POP below knee crease	874	12.2 (106)	874	10.4 (91)	874	3.9 (34)
SUPERFICIAL SYSTEM						
GSV origin	838	9.3 (78)	831	10.6 (81)	815	4.2 (34)
GSV lower thigh	811	17.9 (145)	826	16.8 (139)	784	6.9 (55)
SSV	754	4.5 (34)	771	5.3 (41)	699	1.1 (8)

[a] Missing data for the following reasons: vein segment could not be imaged, absence of blood flow in the vein segment, subjects unable to undergo all or part of the scan due to feeling faint or the examination being performed in their home

% (N) = % (number) with venous reflux ≥ 0.5 seconds duration at baseline

[b] Reflux in both legs calculated as a percentage of participants who had valid reflux measurements for that vein segment in both legs at baseline

CFV = common femoral vein

FV = femoral vein

POP = popliteal vein

GSV = great saphenous vein

SSV = small saphenous vein

TABLE 8.2 PREVALENCE OF REFLUX ≥ 0.5 SECONDS IN INDIVIDUAL VEIN SEGMENT AT BASELINE BY AGE GROUP

	AGE GROUP AT BASELINE					
	18-24 YEARS	25-34 YEARS	35-44 YEARS	45-54 YEARS	55-64 YEARS	P VALUE*
REFLUX AT BASELINE	% (N)	% (N)	% (N)	% (N)	% (N)	
VEIN SEGMENT						
CFV	7.0 (3)	8.5 (10)	13.8 (26)	13.4 (38)	19.1 (46)	<0.05
FV origin	2.4 (1)	7.6 (9)	7.4 (14)	9.5 (27)	11.6 (28)	0.03
FV lower thigh	9.5 (4)	12.7 (15)	11.1 (12)	8.5 (24)	14.5 (35)	0.51
POP above knee crease	14.0 (6)	20.3 (24)	22.2 (42)	17.3 (49)	23.2 (56)	0.41
POP below knee crease	16.3 (7)	20.3 (24)	22.2 (42)	14.8 (42)	20.3 (49)	0.81
GSV origin	7.3 (3)	9.4 (11)	11.3 (21)	16.7 (45)	24.4 (52)	<0.001
GSV lower thigh	15.0 (6)	15.9 (18)	22.4 (41)	27.7 (72)	43.1 (93)	<0.001
SSV	14.3 (5)	4.5 (4)	7.3 (11)	8.0 (19)	14.2 (28)	0.07

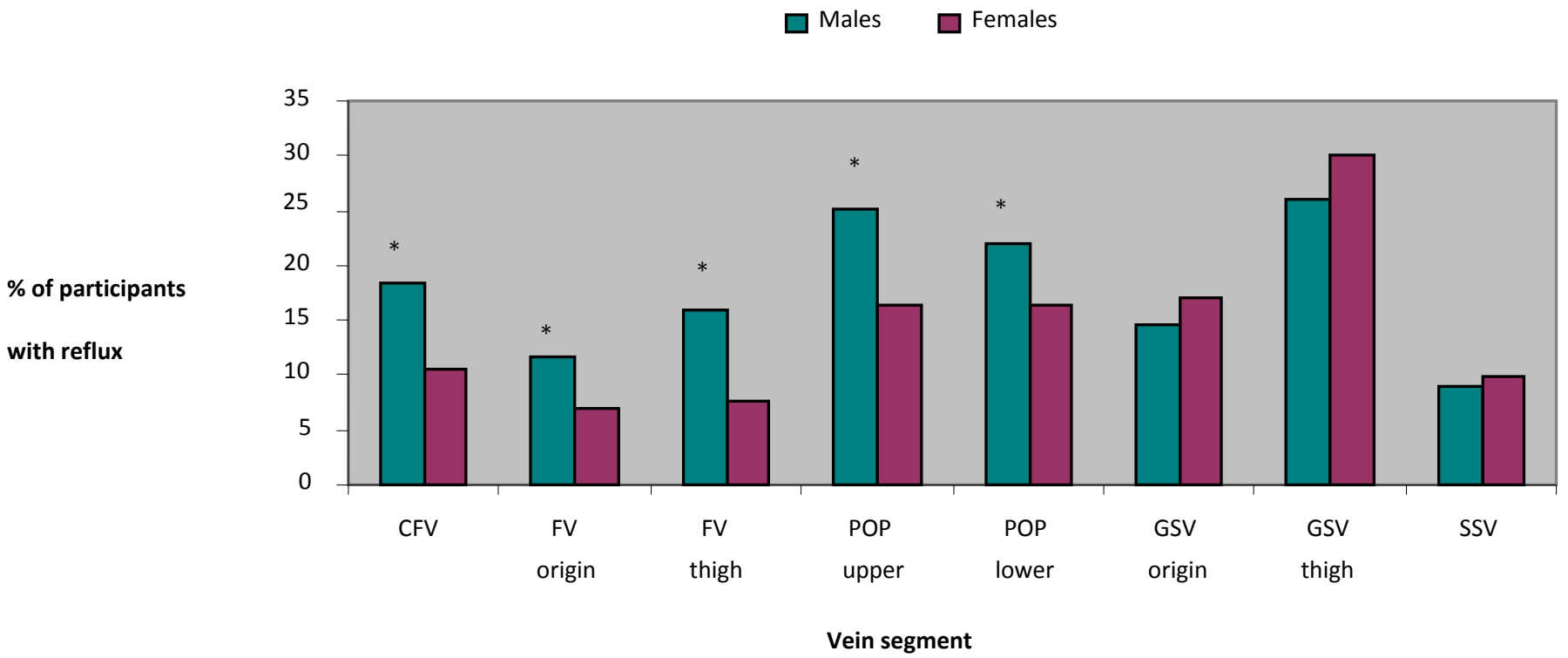
% (N) = % (number) with venous reflux ≥ 0.5 seconds duration at baseline
*P value based on linear test for trend for association between age and prevalence reflux ≥ 0.5 seconds duration in individual vein segment at baseline
CFV = common femoral vein
FV = femoral vein
POP = popliteal vein
GSV = great saphenous vein
SSV = small saphenous vein

TABLE 8.3 PREVALENCE OF REFLUX ≥ 0.5 SECONDS IN VENOUS SYSTEM AT BASELINE BY AGE GROUP

	AGE GROUP AT BASELINE					
	18-24 YEARS	25-34 YEARS	35-44 YEARS	45-54 YEARS	55-64 YEARS	P VALUE*
REFLUX AT BASELINE	% (N)	% (N)	% (N)	% (N)	% (N)	
VENOUS SYSTEM						
No reflux	55.3 (21)	48.5 (47)	41.1 (67)	46.2 (115)	31.1 (66)	0.001
Deep only	16.3 (7)	23.7 (28)	25.4 (48)	16.6 (47)	15.8 (38)	<0.05
Superficial only	10.5 (4)	8.2 (8)	12.9 (21)	17.3 (43)	22.6 (48)	<0.001
Deep and superficial	14.3 (6)	12.5 (14)	15.0 (27)	15.9 (44)	26.3 (60)	0.001

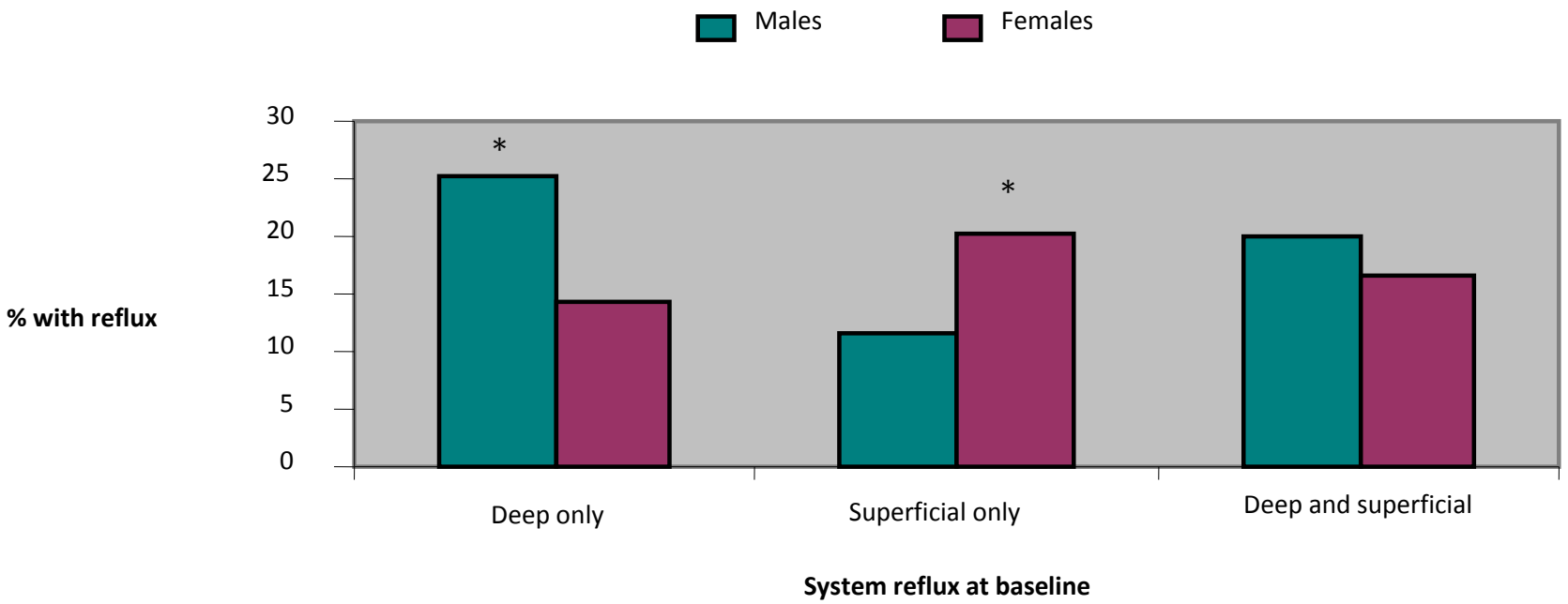
% (N) = % (number) with venous reflux ≥ 0.5 seconds duration at baseline
*P value based on linear test for trend for association between age and prevalence reflux ≥ 0.5 seconds duration in venous system at baseline
Deep only = reflux ≥0.5 seconds duration in CFV, FV or POP and no reflux ≥ 0.5 seconds duration in GSV or SSV in any leg at baseline
Superficial only = reflux ≥0.5 seconds duration in GSV or SSV and no reflux ≥ 0.5 seconds duration in CFV, FV or POP in any leg at baseline
Deep and superficial reflux = reflux ≥0.5 seconds duration in CFV, FV or POP and reflux ≥ 0.5 seconds duration in GSV or SSV in any leg at baseline

FIGURE 8.1 PREVALENCE OF REFLUX ≥ 0.5 SECONDS IN INDIVIDUAL VEIN SEGMENTS AT BASELINE BY SEX



*P<0.05. P value based on chi square test for differences in reflux ≥ 0.5 seconds duration by vein segments at baseline in men and women.

FIGURE 8.2 PREVALENCE OF REFLUX ≥ 0.5 SECONDS BY VENOUS SYSTEM AT BASELINE IN MEN AND WOMEN



*P < 0.05. P value based on chi square test for differences in venous system reflux at baseline in men and women.
Deep only = reflux ≥ 0.5 seconds duration in CFV, FV or POP and no reflux ≥ 0.5 seconds duration in GSV or SSV in any leg at baseline
Superficial only = reflux ≥ 0.5 seconds duration in GSV or SSV and no reflux ≥ 0.5 seconds duration in CFV, FV or POP in any leg at baseline
Deep and superficial = reflux ≥ 0.5 seconds duration in CFV, FV or POP and reflux ≥ 0.5 seconds duration in GSV or SSV in any leg at baseline

TABLE 8.4 PREVALENCE OF REFLUX ≥ 0.5 SECONDS IN RIGHT AND LEFT LEGS SEPARATELY AND IN BOTH LEGS AT FOLLOW UP

	RIGHT LEG		LEFT LEG		BOTH LEGS	
REFLUX AT BASELINE	**TOTAL (N) [a]**	**% (N)**	**TOTAL (N) [a]**	**% (N)**	**TOTAL (N) [b]**	**% (N)**
DEEP SYSTEM						
CFV	876	1.6 (14)	870	2.1 (18)	868	0.5 (4)
FV origin	877	1.6 (14)	875	1.4 (12)	875	1.4 (12)
FV lower thigh	877	2.5 (22)	869	2.0 (17)	869	0.3 (3)
POP above knee crease	879	7.2 (63)	864	5.8 (50)	864	2.3 (20)
POP below knee crease	875	6.9 (60)	860	5.5 (47)	860	1.7 (15)
SUPERFICIAL SYSTEM						
GSV origin	876	15.0 (131)	801	11.7 (94)	801	5.2 (42)
GSV lower thigh	875	21.6 (189)	821	17.2 (141)	821	9.6 (79)
SSV	874	8.4 (73)	833	3.2 (27)	833	1.1 (9)

[a] Missing data: vein segment could not be imaged, absence of blood flow in the vein segments or subjects unable to undergo all or part of the scan due to feeling faint.
[b] Reflux in both legs calculated as a percentage of participants who had valid reflux measurements for that vein segment in both legs at follow up.
% (N) = % (number) with venous reflux ≥ 0.5 seconds duration at follow up
CFV = common femoral vein
FV = femoral vein
POP = popliteal vein
GSV = great saphenous vein
SSV = small saphenous vein

TABLE 8.5 PREVALENCE OF REFLUX ≥ 0.5 SECONDS BY INDIVIDUAL VEIN SEGMENTS BY AGE GROUP AT FOLLOW UP

	AGE GROUP AT FOLLOW UP					
	25-34 YEARS	35-44 YEARS	45-54 YEARS	55-64 YEARS	≥ 65 YEARS	P VALUE*
REFLUX AT FOLLOW UP	% (N)	% (N)	% (N)	% (N)	% (N)	
VEIN SEGMENT						
CFV	6.7 (1)	3.2 (3)	4.3 (7)	2.3 (6)	3.3 (11)	0.59
FV origin	6.7 (1)	2.1 (2)	0 (0)	1.5 (4)	2.1 (7)	0.81
FV lower thigh	6.7 (1)	2.1 (2)	1.9 (3)	4.2 (11)	5.7 (19)	0.07
POP above knee crease	20.0 (3)	3.2 (3)	7.9 (13)	9.7 (25)	14.6 (49)	0.05
POP below knee crease	6.7 (1)	7.4 (7)	6.2 (10)	11.2 (29)	13.6 (45)	0.01
GSV origin	6.7 (1)	10.8 (10)	14.7 (24)	15.3 (27)	34.3 (109)	<0.001
GSV lower thigh	20.0 (3)	13.8 (13)	23.9	19.8 (51)	44.3 (145)	<0.001
SSV	6.7 (1)	9.7 (9)	10.1 (16)	10.2 (26)	13.5 (44)	0.15

% (N) = % (number) with venous reflux ≥ 0.5 seconds duration at follow up
*P value based on linear test for trend for association between age prevalence reflux ≥ 0.5 seconds duration in vein segment at follow up
CFV = common femoral vein
FV = femoral vein
POP = popliteal vein
GSV = great saphenous vein
SSV = small saphenous vein

TABLE 8.6 PREVALENCE OF REFLUX ≥ 0.5 SECONDS IN VENOUS SYSTEM BY AGE GROUP AT FOLLOW UP

	AGE GROUP AT FOLLOW UP					
	25-34 YEARS	35-44 YEARS	45-54 YEARS	55-64 YEARS	≥ 65 YEARS	P VALUE*
REFLUX AT FOLLOW UP	% (N)	% (N)	% (N)	% (N)	% (N)	
VENOUS SYSTEM						
No reflux	73.3 (11)	68.1	65.9 (108)	65.0 (165)	47.2 (154)	<0.001
Deep reflux only	6.7 (1)	8.4 (8)	4.3 (7)	9.3 (24)	4.8 (16)	0.46
Superficial reflux only	6.7 (1)	17.6 (16)	20.9 (34)	17.8 (45)	32.6 (105)	<0.001
Deep and superficial reflux	13.3 (2)	5.5 (5)	9.2 (15)	7.9 (20)	15.9 (51)	0.05

% (N) = % (number) with venous reflux ≥ 0.5 seconds duration at follow up
*P value based on linear test for trend for association between age and prevalence reflux ≥ 0.5 seconds duration in venous system at follow up
Deep reflux only= reflux ≥ 0.5 seconds duration in CFV, FV or POP and no reflux ≥ 0.5 seconds duration in GSV or SSV in any leg at follow up
Superficial reflux = reflux ≥ 0.5 seconds duration in GSV or SSV and no reflux ≥ 0.5 seconds duration in CFV, FV or POP in any leg at follow up
Deep and superficial reflux = reflux ≥ 0.5 seconds duration in CFV, FV or POP and reflux ≥ 0.5 seconds duration in GSV or SSV in any leg at follow up

FIGURE 8.3 PREVALENCE OF REFLUX ≥ 0.5 SECONDS IN INDIVIDUAL VEIN SEGMENTS IN EITHER LEG AT FOLLOW UP BY SEX

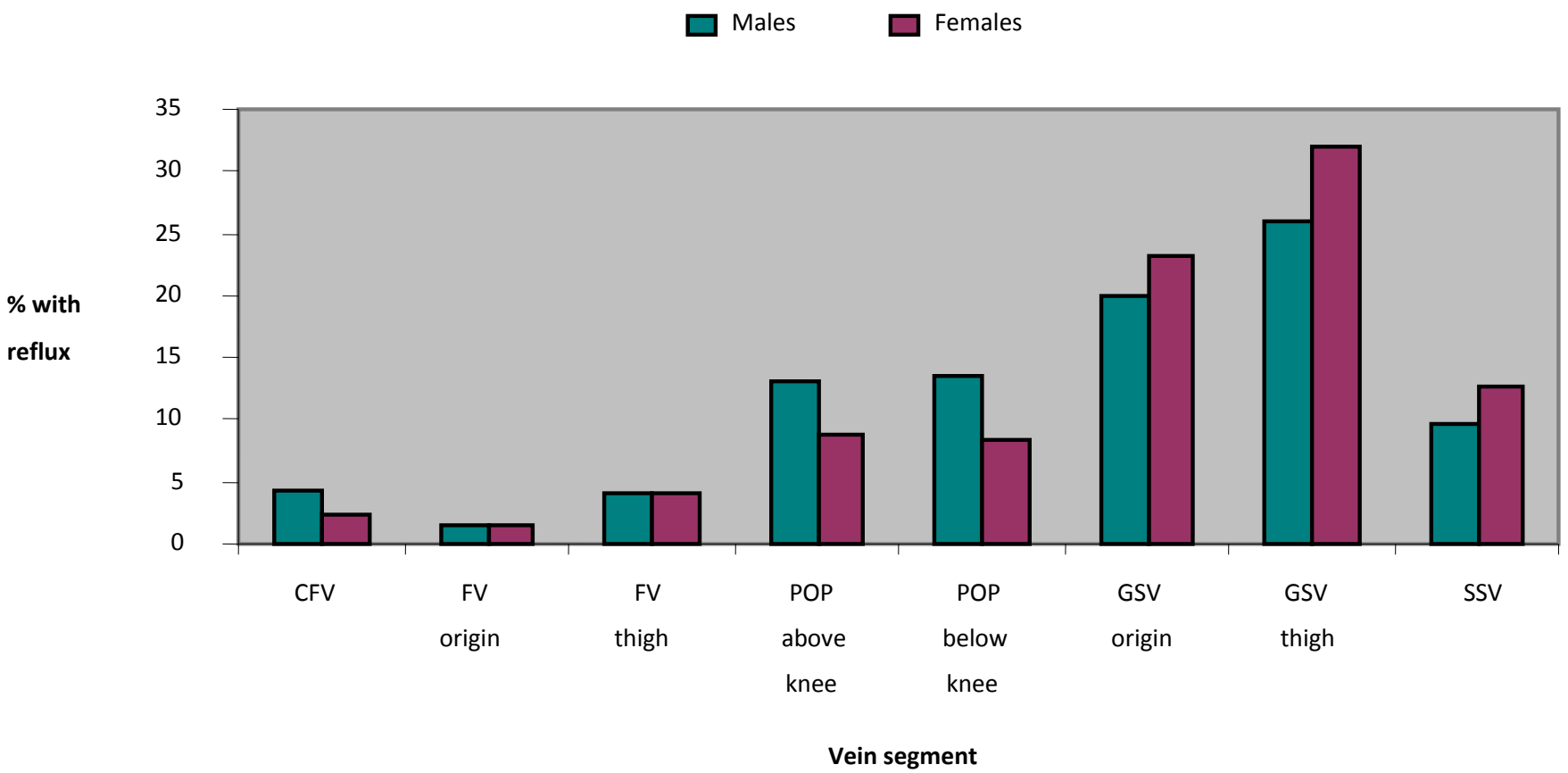
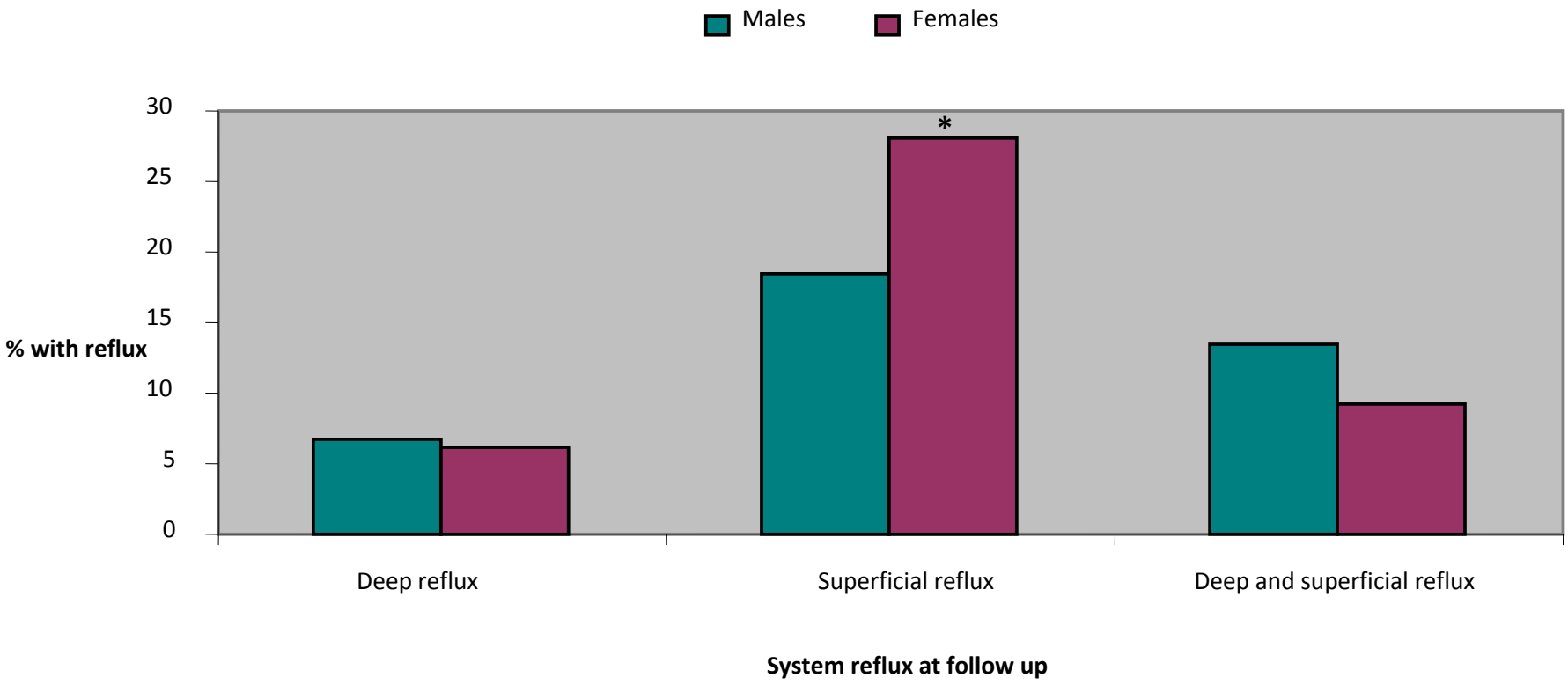


FIGURE 8.4 PREVALENCE OF REFLUX ≥ 0.5 SECONDS BY SYSTEM AT FOLLOW UP IN MEN AND WOMEN



*p<0.001. P value based on chi square test for difference in system reflux at follow up between men and women.
Deep reflux = reflux ≥ 0.5 seconds duration in CFV, FV or POP and no reflux in GSV or SSV in any leg at follow up
Superficial reflux = reflux ≥ 0.5 seconds duration in GSV or SSV and no reflux in CFV, FV or POP in any leg at follow up
Deep and superficial reflux = reflux ≥ 0.5 seconds duration in in CFV, FV or POP and reflux ≥ 0.5 seconds duration in in GSV or SSV in any leg at follow up

TABLE 8.7 13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS AT FOLLOW UP IN THE RIGHT AND LEFT LEGS SEPARATELY AND IN BOTH LEGS TOGETHER

	RIGHT LEG		LEFT LEG		BOTH LEGS	
REFLUX AT FOLLOW UP	**TOTAL (N) [a]**	**% (N)**	**TOTAL (N) [a]**	**TOTAL (N) [a]**	**% (N)**	**TOTAL (N) [a]**
DEEP SYSTEM						
CFV	306	0 (0)	305	0.7 (2)	305	0 (0)
FV origin	306	0 (0)	305	0 (0)	305	0 (0)
FV lower thigh	306	0.3 (1)	305	0 (0)	305	0 (0)
POP above knee crease	306	1.3 (4)	305	0.7 (2)	305	0.3 (1)
POP below knee crease	306	2.3 (7)	305	1.0 (3)	305	0.3 (1)
SUPERFICIAL SYSTEM						
GSV origin	306	2.0 (6)	303	2.3 (7)	303	0.3 (1)
GSV lower thigh	306	4.6 (14)	305	3.9 (12)	305	0.3 (1)
SSV	306	2.3 (7)	302	1.3 (4)	302	0 (0)

% (N) = % (number) with venous reflux ≥ 0.5 seconds duration at follow up

[a] Missing data for the following reasons: vein segment could not be imaged (following vein stripping); absence of blood flow in the vein segments or subjects unable to undergo all or part of the scan due to feeling faint.

[b] Reflux in both legs calculated as a percentage of participants who had valid reflux measurements for that vein segment in both legs at follow up

CFV = common femoral vein

FV = femoral vein

POP = popliteal vein

GSV = great saphenous vein

SSV = small saphenous vein

TABLE 8.8 13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS DURATION IN INDIVIDUAL VEIN SEGMENTS AT FOLLOW UP, BY AGE AT BASELINE

	AGE GROUP AT FOLLOW UP					
	25-34 YEARS	35-44 YEARS	45-54 YEARS	55-64 YEARS	≥ 65 YEARS	P VALUE*
REFLUX AT FOLLOW UP	% (N)	% (N)	% (N)	% (N)	% (N)	
VEIN SEGMENT						
CFV	5.0 (1)	0 (0)	0 (0)	0 (0)	1.6 (1)	0.54
FV origin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-
FV lower thigh	0 (0)	2.1 (1)	0 (0)	0 (0)	0 (0)	0.20
POP above knee crease	0 (0)	0 (0)	1.5 (1)	1.8 (2)	3.1 (2)	0.73
POP below knee crease	0 (0)	2.1 (1)	1.5 (1)	4.4 (5)	3.1 (2)	0.62
GSV origin	5.0 (1)	2.1 (1)	6.1 (4)	1.8 (2)	6.3 (4)	0.78
GSV lower thigh	15.0 (3)	2.1 (1)	6.1 (4)	3.6 (4)	20.0 (13)	0.06
SSV	5.0 (1)	4.3 (2)	1.5 (1)	1.8 (2)	7.9 (5)	0.50

% (N) = % (number) with venous reflux ≥ 0.5 seconds duration at follow up
*P value based on linear test for trend for association between age and incidence of reflux ≥ 0.5 seconds duration in vein segment at follow up
CFV = common femoral vein
FV = femoral vein
POP = popliteal vein
GSV = great saphenous vein
SSV = small saphenous vein

TABLE 8.9 13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS DURATION IN VENOUS SYSTEM AT FOLLOW UP BY AGE AT BASELINE

	AGE GROUP AT FOLLOW UP					
	25-34 YEARS	35-44 YEARS	45-54 YEARS	55-64 YEARS	≥ 65 YEARS	P VALUE*
REFLUX AT FOLLOW UP	% (N)	% (N)	% (N)	% (N)	% (N)	
VENOUS SYSTEM						
No reflux	0 (0)	0 (0)	0 (0)	0.9 (1)	4.8 (3)	0.13
Deep reflux only	5.0 (1)	4.3 (2)	1.5 (1)	3.6 (4)	0 (0)	0.30
Superficial reflux only	15.0 (3)	6.4 (3)	7.6 (5)	5.5 (6)	15.6 (10)	0.52
Deep and superficial reflux	20.0 (4)	10.6 (5)	9.1 (6)	10.1 (11)	20.3 (13)	0.48

% (N) = % (number) with venous reflux ≥ 0.5 seconds duration at follow up
*P value based on linear test for trend for association between age and incidence of reflux ≥ 0.5 seconds duration at follow up
Deep reflux only = reflux ≥ 0.5 seconds duration in CFV, FV or POP and no reflux ≥ 0.5 seconds duration in GSV or SSV in any leg at baseline
Superficial reflux only = reflux ≥ 0.5 seconds duration in GSV or SSV and no reflux ≥ 0.5 seconds duration in CFV, FV or POP in any leg at baseline
Deep and superficial reflux = reflux ≥ 0.5 seconds duration in CFV, FV or POP and reflux ≥ 0.5 seconds duration in GSV or SSV in any leg at baseline

CHAPTER 9: PREVALENCE OF VENOUS REFLUX AND INCIDENCE OF CHRONIC VENOUS DISEASE

9.1 CHAPTER OUTLINE

Evidence suggests that venous reflux, thought to occur as a result of damaged valves, causes veins to enlarge and become varicose. Venous reflux is a progressive condition and if left untreated, can lead to more severe disease. This chapter examines the association between the prevalence of reflux ≥ 0.5 s at baseline and the incidence of C2 varicose veins and C3-C6 CVI at follow up. The incidence of varicose veins and CVI will be presented separately and analysed according to reflux in specific vein segments, number of segments and venous system affected. The association between reflux and severity of C2 varices will be measured. Due to the low incidence of CVI at follow up, it was not possible to examine the association between reflux and severity of CVI.

The incidence reported in this chapter is leg-specific. Therefore only cases where reflux at baseline and the development of C2 varices or C3-C6 CVI occurred in the same leg are considered. In determining the incidence of C2 varices at follow up, the leg with the highest Basle grade for severity was chosen. For measuring the incidence of CVI, the highest C3-C6 CEAP class was chosen. Within the C4 class, which is split into two categories, the most severe condition was chosen. For C2 varices and CVI, if the severity of disease was equal in both legs, then either the right or left leg was selected at random and included in the analysis.

9.2 PREVALENCE OF VENOUS REFLUX AND INCIDENCE OF C2 VARICOSE VEINS

9.2.1 Any reflux

To examine the relationship between prevalence of venous reflux ≥ 0.5s at baseline and incidence of C2 varicose veins at follow up, participants free of C2 varices at baseline were selected (n=555). Ninety four participants with missing reflux data were excluded from the analysis. Of 461 participants with valid reflux data, 204 (44.3%) had some reflux at baseline, 48 of whom developed C2 varices at follow up, resulting in a 13-year incidence of 23.5% (95% CI 17.5-30.9). This was significantly higher than the incidence of C2 varices in those with no reflux at baseline 12.8% (95% CI 9.0-17.8) (P=0.004). When analysed by leg, the 13-year incidence was 20.0% (95% CI 11.8-31.8) in the right leg, 18.6% (95% CI 10.3-31.0) and 13.0% (95% CI 5.7-25.6) in both legs.

9.2.2 Reflux by venous system

Tables 9.1 and 9.2 show the 13 year leg-specific incidences of C2 varicose veins according to system reflux at baseline, for the right and left legs respectively. Reflux confined to the deep veins only was not associated with the development of C2 varices in either leg (both $p>0.05$). However reflux in the superficial system at baseline was associated with increased incidence of C2 varices and this was significant for both legs (both $p<0.05$). After adjusting for age and sex, the odds of developing C2 varices if reflux was present in the superficial system were 4.4 (95% CI 1.8-10.8) in the right leg and 2.6 (95% CI 1.2-6.0) in the left leg. The odds ratios for C2 varices in those with combined deep and superficial reflux were higher still at 7.3 (95% CI 2.6-22.6) and 4.0 (95% CI 1.3-17.2) for the right and left legs respectively.

9.2.3 Reflux by vein segment

The 13-year leg-specific incidence of C2 varicose veins of any severity in the right leg by reflux ≥ 0.5 s in individual vein segments at baseline is shown in Tables 9.3. Of the deep veins scanned, reflux in the FV in the lower thigh and in the POP vein above and below the knee crease, were all significantly associated with increased incidence of C2 varices (all $p<0.05$). After adjusting for age and sex, participants with reflux in these segments were between 2.7 and 3.7 times more likely to develop C2 varices than those with no reflux in these segments at baseline. Reflux in the GSV was also significantly associated with an increased incidence of C2 varices ($p<0.001$). The age- and sex-adjusted risk of developing C2 varices was 5.8 (95% CI 1.2-27.3) fold in those with reflux in origin of this vein and higher still at 7.1 (95% CI 3.1-16.3) in those with reflux in this vein in the lower third of the thigh.

Table 9.4 presents the 13-year leg-specific incidence of C2 varices in the left leg by reflux in individual vein segments at baseline. The only deep vein significantly associated with an increased incidence of C2 varices was the POP vein below the knee crease. After adjusting for age and sex, participants with reflux in this segment at baseline were 2.6 (95% CI 1.0-6.2) times more likely to have C2 varices at follow up. Reflux in the GSV origin and in the lower third of the thigh was also significantly associated with the incidence of C2 varices ($p=0.006$ and $p=0.003$ respectively). When reflux was present in either of these two segments at baseline, the risk of developing C2 varices over the 13 year follow up period was three to fourfold (both $p<0.05$) Reflux in the SSV was not significantly associated with the incidence of C2 varices ($p=0.31$)

9.2.4 Reflux by number of vein segments

Tables 9.5 and 9.6 presents the leg-specific incidence of C2 varices according to the number of vein segments with reflux at baseline in the right and left legs. In the right leg, the incidence of C2 varices of any severity was 9.5% (95% CI 6.9-12.7) in those with no reflux and increased with number of segment affected so that in those with reflux in 3 or more deep segments, the incidence was 35.3% (95% CI 14.3-73.4) (P trend<0.01). For superficial veins, the incidence of C2 varices was over 7 fold in those with reflux in 2 segments (42.9%, 95% CI 10.9-116.6) compared to those with no reflux (8.8%, 95% CI 6.3-12.0) (p trend<0.001). In the left leg, there was no significant association between number of refluxing deep segments and incidence of C2 varices (p trend<0.15). However, for superficial veins the incidence of C2 varices increased linearly from 10.7% (95% CI 7.9-14.1), to 21.2% (95% CI 9.3-41.9) to 37.5% (95% CI 15.2-78.0) in those with 0, 1 and 2 refluxing segments respectively (p trend<0.001). Statistical tests on the severity of C2 varices must be interpreted with caution due to the small sample with grade 2 and 3 varices.

Analyses on the severity of C2 varices at follow up, according to reflux ≥ 0.5s in specific vein segments at baseline in the right and left legs are displayed in Table 9.7 and 9.8 respectively. Again the statistical tests must be interpreted with caution. The majority of new cases of C2 varices at follow up were classified as mild (grade 1). As very few participants with reflux at baseline developed moderate (grade 2) and severe (grade 3) C2 varices at follow up, the sample is too small to estimate the incidence with precision and therefore conclusions cannot really be drawn from the results.

9.3 PREVALENCE OF VENOUS REFLUX AND INCIDENCE OF C3-C6 CVI

9.3.1 Any reflux

To determine the incidence of C3-C6 CVI by reflux at baseline, participants free of CVI at baseline were selected (n=546). Reflux data was available for 454 participants, of whom 198 had reflux. Of those, 20 participants developed new C3-C6 CVI at follow up, resulting in a 13-year incidence of 10.1% (95% CI 6.3-15.3). The incidence of CVI in those without reflux at baseline was not significantly different (9.8%, 95% CI 6.4-14.2) (p=0.59).

9.3.2 Reflux by venous system

The 13-year leg-specific incidences of C3-C6 CVI at follow up by venous system reflux ≥ 0.5 s at baseline are presented in Tables 9.9 and 9.10. Deep, superficial nor combined reflux were significantly associated with increased incidence of CVI in either leg at follow up (all p>0.05). However, the number of participants with reflux and CVI was very small and thus it is difficult to draw any meaningful conclusions.

9.3.3 Reflux by specific vein segments

Reflux in superficial vein segments was not associated with incidence of CVI (all p>0.05) [Tables 9.11 and 9.12]. Unlike C2 varicose veins, reflux in the GSV had no significant association with the development of CVI. The age- and sex-adjusted odds ratios were 1.5 (95% CI 0.2-13.5) and 1.4 (95% CI 0.4-4.9) in the GSV origin and in the lower third of the thigh respectively. It is important to note that the number of participants with reflux at baseline who subsequently developed CVI at follow up is too small to estimate the incidence with precision.

9.4 CHAPTER SUMMARY

The analysis in this chapter has shown that those with venous reflux, particularly in the GSV of the superficial system, were at significantly increased risk of developing C2 varicose veins at follow up. Additionally, those with combined reflux in the deep and superficial systems were at greatest risk of acquiring C2 varices. The presence of reflux appeared to have no significant effect on the incidence of CVI. However, the number of participants who developed CVI was too small to precisely estimate the incidence of this condition. The chapter has presented univariate analyses on the association of reflux at baseline and incidence of C2 varicose veins and C3-C6 CVI at follow up. The next chapter will present univariate analyses on the association of risk factors at baseline and incidence of C2 varicose veins and C3-C6 CVI at follow up. Any reflux or risk factor significant on univariate analysis will be entered into a logistic regression model to determine which factors remained independently significant for the incidence of either condition. The results of this multivariate analysis will be presented at the end of Chapter 10.

TABLE 9.1 13 YEAR INCIDENCE OF C2 VARICOSE VEINS IN RIGHT LEG BY PRESENCE OF REFLUX ≥ 0.5 SECONDS DURATION BY VENOUS SYSTEM IN RIGHT LEG AT BASELINE

	13 YEAR INCIDENCE C2 VARICOSE VEINS		P VALUE*	UNADJUSTED ODDS RATIO [a]	ADJUSTED ODDS RATIO [b]
REFLUX AT BASELINE	% (95% CI)	n (N)			
DEEP REFLUX [1]					
- No	10.5 (7.8-13.8)	48 (457)	0.10	1.00	1.00
- Yes	17.0 (10.1-27.1)	16 (94)		1.75 (0.94-3.23)	1.82 (0.98-3.41)
SUPERFICIAL REFLUX [2]					
- No	10.7 (8.0-14.1)	48 (448)	0.01	1.00	1.00
- Yes	34.6 (16.9-63.5)	9 (26)		4.41 (1.86-10.44)	4.43 (1.82-10.79)
DEEP + SUPERFICIAL [3]					
- No	10.4 (7.9-13.5)	55 (27)	0.01	1.00	1.00
- Yes	42.9 (17.4-89.1)	6 (14)		6.44 (2.15-19.23)	7.30 (2.36-22.55)

% (95% CI) 13 year incidence (95% confidence interval) of C2 varicose veins

n = number of participants in reflux group at baseline with C2 varicose veins at follow up, (N) = number in reflux group at baseline

*P value based on chi square test for difference in incidence of C2 varicose veins by presence of reflux ≥ 0.5s in venous system at baseline

[a] Unadjusted odds ratio = crude odds ratio with no adjustments for age and sex

[b] Adjusted odds ratio = adjusted for age and sex

[1] Deep reflux = reflux ≥ 0.5s in CFV, FV origin, FV lower thigh, POP upper or POP lower and no reflux in GSV origin, GSV lower thigh or SSV

[2] Superficial reflux= reflux ≥ 0.5s in GSV origin, GSV lower thigh or SSV and no reflux in CFV, FV origin, FV lower thigh, POP upper or POP lower

[3] Combined reflux = reflux ≥ 0.5s in CFV, FV origin, FV lower thigh, POP upper or POP lower and reflux ≥ 0.5s in GSV origin, GSV lower thigh or SSV

TABLE 9.2 13 YEAR INCIDENCE OF C2 VARICOSE VEINS IN LEFT LEG BY PRESENCE OF REFLUX ≥ 0.5 SECONDS DURATION BY VENOUS SYSTEM IN LEFT LEG AT BASELINE

	13 YEAR INCIDENCE C2 VARICOSE VEINS		P VALUE*	UNADJUSTED ODDS RATIO [a]	ADJUSTED ODDS RATIO [b]
REFLUX AT BASELINE	**% (95% CI)**	**n (N)**			
DEEP REFLUX [1]					
- No	11.8 (9.3-15.8)	56 (457)	0.95	1.00	1.00
- Yes	12.0 (5.9-22.0)	9 (75)		1.02 (0.48-2.17)	1.09 (0.49-2.38)
SUPERFICIAL REFLUX [2]					
- No	10.7 (8.0-14.1)	48 (448)	0.01	1.00	1.00
- Yes	25.6 (13.0-45.7)	10 (39)		2.82 (1.30-6.14)	2.64 (1.16-5.99)
DEEP + SUPERFICIAL [3]					
- No	11.7 (9.1-15.0)	62 (527)	0.01	1.00	1.00
- Yes	30.0 (7.6-81.6)	3 (10)		3.25 (1.22-12.89)	4.01 (1.33-17.24)

% (95% CI) 13 year incidence (95% confidence interval) of C2 varicose veins
n = number of participants in reflux group at baseline with C2 varicose veins at follow up, (N) = number in reflux group at baseline
*P value based on chi square test for difference in incidence of C2 varicose veins by presence of reflux ≥ 0.5s in venous system at baseline
[a] Unadjusted odds ratio = crude odds ratio with no adjustments for age and sex
[b] Adjusted odds ratio = adjusted for age and sex
[1] Deep reflux = reflux ≥ 0.5s in CFV, FV origin, FV lower thigh, POP upper or POP lower and no reflux in GSV origin, GSV lower thigh or SSV
[2] Superficial reflux= reflux ≥ 0.5s in GSV origin, GSV lower thigh or SSV and no reflux in CFV, FV origin, FV lower thigh, POP upper or POP lower
[3] Combined reflux = reflux ≥ 0.5s in CFV, FV origin, FV lower thigh, POP upper or POP lower and reflux ≥ 0.5s in GSV origin, GSV lower thigh or SSV

TABLE 9.3 13 YEAR INCIDENCE OF C2 VARICOSE VEINS IN RIGHT LEG BY PRESENCE OF REFLUX ≥ 0.5 SECONDS DURATION BY VEIN SEGMENT IN RIGHT LEG AT BASELINE

	13 YEAR INCIDENCE C2 VARICOSE VEINS		P VALUE*	UNADJUSTED ODDS RATIO [a]	ADJUSTED ODDS RATIO [b]
REFLUX AT BASELINE	**% (95% CI)**	**n (N)**			
CFV [1]					
- No	11.4 (8.9-14.6)	60 (526)	0.33	1.00	1.00
- Yes	16.0 (5.1-38.6)	4 (25)		1.48 (0.49-4.45)	1.57 (0.51-4.81)
FV [2]					
- No	11.1 (8.5-14.3)	58 (521)	0.12	1.00	1.00
- Yes	20.0 (8.1-41.6)	6 (30)		2.00 (0.78-5.08)	2.08 (0.80-5.38)
FV LOWER					
- No	10.8 (8.3-13.9)	57 (526)	0.02	1.00	1.00
- Yes	28.0 (12.2-55.4)	7 (25)		3.20 (1.28-8.00)	3.74 (1.45-9.67)
POP ABOVE KNEE [3]					1.00
- No	10.3 (7.8-13.4)	52 (505)	0.03	1.00	
- Yes	26.1 (14.1-44.3)	12 (46)		3.08 (1.50-6.30)	3.22 (1.56-6.67)
POP BELOW KNEE					
- No	10.4 (7.9-13.6)	52 (499)	0.01	1.00	1.00
- Yes	23.1 (12.5-39.2)	12 (52)		2.58 (1.28-5.22)	2.68 (1.31-5.50)

% (95% CI) 13 year incidence (95% confidence interval) of C2 varicose veins

n = number of participants in reflux group at baseline with C2 varicose veins at follow up, (N) = number in reflux group at baseline

*P value based on chi square test for difference in incidence of C2 varicose veins by presence of reflux ≥ 0.5s in vein segment at baseline

[a] Unadjusted odds ratio = crude odds ratio with no adjustments for age and sex

[b] Adjusted odds ratio = adjusted for age and sex

[1] CFV = common femoral vein

[2] FV = femoral vein

[3] POP = popliteal vein

TABLE 9.3 13 YEAR INCIDENCE OF C2 VARICOSE VEINS IN RIGHT LEG BY PRESENCE OF REFLUX ≥ 0.5 SECONDS DURATION BY VEIN SEGMENT IN RIGHT LEG AT BASELINE

	13 YEAR INCIDENCE C2 VARICOSE VEINS		P VALUE*	UNADJUSTED ODDS RATIO [a]	ADJUSTED ODDS RATIO [b]
REFLUX AT BASELINE	**% (95% CI)**	**n (N)**			
GSV ORIGIN [1]					
- No	10.7 (8.2-13.7)	57 (533)	0.03	1.00	1.00
- Yes	42.9 (10.9-116.6)	3 (7)		6.26 (1.37-28.70)	5.80 (1.23-27.33)
GSV THIGH					
- No	9.1 (6.7-12.1)	45 (492)	<0.001	1.00	1.00
- Yes	40.0 (21.7-68.0)	12 (30)		6.62 (3.00-14.62)	7.12 (3.11-16.26)
SSV THIGH [2]					
- No	11.4 (8.6-14.8)	53 (465)	0.10	1.00	1.00
- Yes	30.0 (7.6-81.6)	3 (10)		3.33 (0.84-13.28)	3.19 (0.78-13.02)

% (95% CI) 13 year incidence (95% confidence interval) of C2 varicose veins

n = number of participants in reflux group at baseline with C2 varicose veins at follow up, (N) = number in reflux group at baseline

*P value based on chi square test for difference in incidence of C2 varicose veins by presence of reflux ≥ 0.5s in vein segment at baseline

[a] Unadjusted odds ratio = crude odds ratio with no adjustments for age and sex

[b] Adjusted odds ratio = adjusted for age and sex

[1] GSV = great saphenous vein

[2] SSV = short saphenous vein

TABLE 9.4 13 YEAR INCIDENCE OF C2 VARICOSE VEINS IN LEFT LEG BY PRESENCE OF REFLUX ≥ 0.5 SECONDS DURATION BY VEIN SEGMENT IN LEFT LEG AT BASELINE

	13 YEAR INCIDENCE C2 VARICOSE VEINS		P VALUE*	UNADJUSTED ODDS RATIO [a]	ADJUSTED ODDS RATIO [b]
REFLUX AT BASELINE	**% (95% CI)**	**n (N)**			
CFV [1]					
- No	12.0 (8.9-14.6)	63 (526)	0.42	1.00	1.00
- Yes	8.0 (5.1-38.6)	2 (25)		0.64 (0.15-2.78)	0.65 (0.14-2.90)
FV [2]					
- No	11.7 (8.5-14.3)	63 (537)	0.51	1.00	1.00
- Yes	14.3 (8.1-41.6)	2 (14)		1.25 (0.27-5.73)	1.01 (0.21-4.84)
FV LOWER THIGH					
- No	11.5 (8.3-13.9)	61 (530)	0.23	1.00	1.00
- Yes	19.0 (12.2-55.4)	4 (21)		1.81 (0.59-5.55)	2.59 (0.78-8.53)
POP ABOVE KNEE [3]					
- No	11.2 (7.8-13.4)	57 (510)	0.09	1.00	1.00
- Yes	19.5 (14.1-44.3)	8 (41)		1.93 (0.85-4.38)	2.27 (0.95-5.40)
POP BELOW KNEE					
- No	11.1 (7.9-13.6)	57 (512)	0.07	1.00	1.00
- Yes	20.5 (12.5-39.2)	8 (39)		2.06 (0.90-4.70)	2.55 (1.05-6.17)

% (95% CI) 13 year incidence (95% confidence interval) of C2 varicose veins

n = number of participants in reflux group at baseline with C2 varicose veins at follow up, (N) = number in reflux group at baseline

*P value based on chi square test for difference in incidence of C2 varicose veins by presence of reflux ≥ 0.5s in vein segment at baseline

[a] Unadjusted odds ratio = crude odds ratio with no adjustments for age and sex

[b] Adjusted odds ratio = adjusted for age and sex

[1] CFV = common femoral vein

[2] FV = femoral vein

[3] POP = popliteal vein

TABLE 9.4 13 YEAR INCIDENCE OF C2 VARICOSE VEINS IN LEFT LEG BY PRESENCE OF REFLUX ≥ 0.5 SECONDS DURATION BY VEIN SEGMENT IN LEFT LEG AT BASELINE

REFLUX AT BASELINE	13 YEAR INCIDENCE C2 VARICOSE VEINS % (95% CI)	n (N)	P VALUE*	UNADJUSTED ODDS RATIO [a]	ADJUSTED ODDS RATIO [b]
GSV ORIGIN [1]					
- No	10.9 (8.2-13.7)	57 (525)	0.01	1.00	1.00
- Yes	37.5 (10.9-116.6)	6 16		4.93 (1.73-14.06)	4.45 (1.47-13.51)
GSV THIGH					
- No	10.2 (6.7-12.1)	51 (498)	0.01	1.00	1.00
- Yes	27.5 (21.7-68.0)	11 (40)		3.32 (1.57-7.05)	3.14 (1.43-6.92)
SSV THIGH [2]					
- No	12.3 (8.6-14.8)	58 (472)	0.31	1.00	1.00
- Yes	22.2 (7.6-81.6)	2 (9)		2.04 (0.41-10.05)	2.62 (0.47-14.52)

% (95% CI) 13 year incidence (95% confidence interval) of C2 varicose veins
n = number of participants in reflux group at baseline with C2 varicose veins at follow up, (N) = number in reflux group at baseline
*P value based on chi square test for difference in incidence of C2 varicose veins by presence of reflux ≥ 0.5s in vein segment at baseline
[a] Unadjusted odds ratio = crude odds ratio with no adjustments for age and sex
[b] Adjusted odds ratio = adjusted for age and sex
[1] GSV = great saphenous vein
[2] SSV = short saphenous vein

TABLE 9.5 13 YEAR INCIDENCE OF C2 VARICOSE VEINS BY GRADE IN RIGHT LEG ACCORDING TO NUMBER OF VEIN SEGMENTS WITH REFLUX ≥ 0.5 SECONDS DURATION AT BASELINE IN RIGHT LEG

	13 YEAR INCIDENCE OF C2 VARICOSE VEINS							
NUMBER OF VEIN SEGMENTS	**ANY GRADE**		**GRADE 1**		**GRADE 2**		**GRADE 3**	
WITH REFLUX AT BASELINE	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**	**% (95% CI)**	**N**
DEEP VEINS								
0 (n=443)	9.5 (6.9-12.7)	42	8.6% (6.1-11.6)	38	0.7% (0.2-1.8)	3	0.22% (0.1-1.1)	1
1 (n=59)	16.9 (8.6-30.2)	10	17.6% (7.4-28.0)	9	2.0% (0.8-8.3)	1	0% (0)	0
2 (n=32)	18.8 (7.6-39.0)	6	15.6% (5.7-34.6)	5	3.1% (0.2-15.4)	1	0% (0)	0
≥ 3 (n=17)	35.3 (14.3-73.4)	6	23.1% (7.5-56.8)	4	15.4% (2.0-38.9)	2	0% (0)	0
P VALUE*	<0.001		0.14		0.48		0.10	
SUPERFICIAL VEINS								
0 (n=419)	8.8 (6.3-12.0)	37	7.9% (5.5-10.9)	33	0.7% (0.2-1.9)	3	0.2% (0.1-1.1)	1
1 (n=33)	36.4 (19.7-61.8)	12	33.3% (17.5-57.9)	11	3.0% (0.2-14.9)	1	0% (0)	0
2 (n=7)	42.9 (10.9-116.6)	3	28.6% (4.8-94.3)	2	14.3% (0.7-70.4)	1	0% (0)	0
P VALUE*	<0.001		0.28		0.39		0.13	

% (95% CI) 13 year incidence (95% confidence interval) of C2 varicose veins

N = number of participants in reflux group at baseline with C2 varicose veins at follow up, (n) = number in reflux group at baseline

*P value based on linear test for trend for association between number of vein segments with reflux ≥ 0.5 s at baseline and incidence of new C2 varicose veins at follow up.

TABLE 9.6 13 YEAR INCIDENCE OF C2 VARICOSE VEINS BY GRADE IN LEFT LEG ACCORDING TO NUMBER OF VEIN SEGMENTS WITH REFLUX ≥ 0.5 SECONDS DURATION AT BASELINE IN LEFT LEG

	13 YEAR INCIDENCE OF C2 VARICOSE VEINS							
NUMBER OF VEIN SEGMENTS	ANY GRADE		GRADE 1		GRADE 2		GRADE 3	
WITH REFLUX AT BASELINE	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N
DEEP VEINS								
0 (n=466)	11.4 (8.6-14.8)	53	10.1 (7.5-13.3)	47	1.3 (0.5-2.7)	6	0	0
1 (n=47)	4.3 (0.7-14.0)	2	4.3 (0.7-14.0)	2	0	0	0	0
2 (n=24)	33.3 (15.5-63.6)	8	29.2 (12.7-57.7)	7	0	0	4.2 (0.2-20.5)	1
≥ 3 (n=14)	14.3 (2.4-47.2)	2	14.3 (2.4-47.2)	2	0	0	0	0
P VALUE*	0.15		0.13		0.34		0.10	
SUPERFICIAL VEINS								
0 (n=430)	10.7 (7.9-14.1)	46	9.8 (7.1-13.1)	42	0.7 (0.2-1.9)	3	0.2 (0.1-1.1)	1
1 (n=33)	21.2 (9.3-41.9)	7	21.2 (9.3-41.9)	7	0	0	0	0
2 (n=16)	37.5 (15.2-78.0)	6	18.8 (4.8-51.0)	3	18.8 (4.8-51.0)	3	0	0
P VALUE*	<0.001		0.37		0.06		0.18	

% (95% CI) 13 year incidence (95% confidence interval) of C2 varicose veins

N = number of participants in reflux group at baseline with C2 varicose veins at follow up, (n) = number in reflux group at baseline

*P value based on linear test for trend for association between number of vein segments with reflux ≥ 0.5 s at baseline and incidence of new C2 varicose veins at follow up.

TABLE 9.7 13 YEAR INCIDENCE OF C2 VARICOSE VEINS IN RIGHT LEG BY REFLUX ≥ 0.5 S IN VEIN SEGMENTS IN RIGHT LEG AT BASELINE

	13-YEAR INCIDENCE OF C2 VARICOSE VEINS								
	ANY GRADE		GRADE 1		GRADE 2		GRADE 3		P VALUE*
REFLUX AT BASELINE	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	
DEEP VEINS									
[1] CFV (n=25)	16.0 (5.1-38.6)	4	16.0 (5.1-38.6)	4	0	0	0	0	0.72
[2] FV origin (n=30)	23.3 (10.2-46.1)	7	20.0 (8.1-41.6)	6	2.0 (0.2-16.4)	1	0	0	0.33
[3] FV lower thigh (n=25)	28.0 (12.2-55.4)	7	20.0 (7.3-44.3)	5	8.0 (1.3-26.4)	2	0	0	0.003
[4] POP upper (n=46)	26.1 (14.1-44.3)	12	19.6 (9.5-35.9)	9	6.5 (1.7-17.8)	3	0	0	<0.001
[5] POP lower (n=52)	23.1 (12.5-39.2)	12	15.4 (7.1-29.2)	8	7.7 (2.4-18.6)	4	0	0	0.001
SUPERFICIAL VEINS									
[6] GSV origin (n=7)	42.9 (10.9-116.7)	3	28.6 (4.8-94.3)	2	16.7 (0.7-70.4)	1	0	0	0.002
[7] GSV lower thigh (n=30)	33.3 (16.9-59.4)	18	33.3 (16.9-59.4)	10	6.7 (1.1-22.0)	2	0	0	<0.001
[8] SSV (n=10)	30.0 (7.6-81.6)	3	30.0 (7.6-81.6)	3	0	0	0	0	0.15

% (95% CI) 13 year incidence (95% confidence interval) of C2 varicose veins

N = number of participants in reflux group at baseline with C2 varicose veins at follow up, (n) = number in reflux group at baseline

*P value based on linear test for trend for association between number of vein segments with reflux ≥ 0.5 s at baseline and incidence of new C2 varicose veins at follow up.

[1] CFV = common femoral vein

[2] FV origin = femoral vein at origin

[3] FV lower thigh = femoral vein in the lower third of the thigh

[4] POP upper = popliteal vein above the knee

[5] POP lower = popliteal vein below the knee

[6] GSV junction = great saphenous vein at the saphenofemoral junction

[7] GSV lower thigh = great saphenous vein in the lower third of the thigh

[8] SSV = small saphenous vein

TABLE 9.8 13 YEAR INCIDENCE OF C2 VARICOSE VEINS IN LEFT LEG BY REFLUX ≥ 0.5 S IN VEIN SEGMENTS IN LEFT LEG AT BASELINE

	13-YEAR INCIDENCE OF C2 VARICOSE VEINS								
	ANY GRADE		GRADE 1		GRADE 2		GRADE 3		P VALUE*
REFLUX AT BASELINE	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	
DEEP VEINS									
[1] CFV (n=25)	8.0 (1.3-26.4)	2	8.0 (1.3-26.4)	2	0	0	0	0	0.50
[2] FV origin (n=14)	14.3 (2.4-47.2)	2	14.3 (2.4-47.2)	2	0	0	0	0	0.92
[3] FV lower thigh (n=21)	19.0 (6.1-45.6)	4	19.0 (6.1-45.6)	4	0	0	0	0	0.48
[4] POP upper (n=41)	17.4 (9.1-37.1)	8	17.1 (7.5-33.8)	7	0	0	2.4 (0.1-12.0)	1	0.05
[5] POP lower (n=39)	20.5 (9.5-38.9)	8	17.9 (7.8-35.5)	7	0	0	2.6 (0.1-12.6)	1	0.04
SUPERFICIAL VEINS									
[6] GSV origin (n=16)	37.5 (15.2-80.0)	6	18.7 (4.8-51.0)	3	18.7 (4.8-51.0)	3	0	0	<0.001
[7] GSV lower thigh (n=40)	27.5 (14.5-47.8)	11	20.0 (9.3-38.0)	8	7.5 (1.9-20.4)	3	0	0	<0.001
[8] SSV (n=9)	22.2 (3.7-73.4)	2	22.2 (3.7-73.4)	2	0	0	0	0	0.54

% (95% CI) 13 year incidence (95% confidence interval) of C2 varicose veins

N = number of participants in reflux group at baseline with C2 varicose veins at follow up, (n) = number in reflux group at baseline

*P value based on linear test for trend for association between number of vein segments with reflux ≥ 0.5 s at baseline and incidence of new C2 varicose veins at follow up.

[1] CFV = common femoral vein

[2] FV origin = femoral vein at origin

[3] FV lower thigh = femoral vein in the lower third of the thigh

[4] POP upper = popliteal vein above the knee

[5] POP lower = popliteal vein below the knee

[6] GSV origin = great saphenous vein at the saphenofemoral junction

[7] GSV lower thigh = great saphenous vein in the lower third of the thigh

[8] SSV = small saphenous vein

TABLE 9.9 13 YEAR INCIDENCE OF C3-C6 CVI IN RIGHT LEG AT FOLLOW UP BY PRESENCE OF REFLUX ≥ 0.5 SECONDS IN RIGHT LEG AT BASELINE

	13 YEAR INCIDENCE C3-C6 CVI		P VALUE*	UNADJUSTED ODDS RATIO [a]	ADJUSTED ODDS RATIO [b]
REFLUX AT BASELINE	% (95% CI)	n (N)			
DEEP REFLUX [1]					
- No	6.7 (4.6-9.4)	30 (451)	0.61	1.00	1.00
- Yes	8.8 (4.1-16.7)	8 (91)		1.35 (0.60-3.06)	1.55 (0.67-3.60)
SUPERFICIAL REFLUX [2]					
- No	6.8 (4.7-9.6)	30 (441)	0.11	1.00	1.00
- Yes	15.4 (4.9-37.1)	4 (26)		2.49 (0.81-7.70)	1.90 (0.59-6.07)
DEEP + SUPERFICIAL [3]					
- No	6.9 (4.9-9.5)	36 (519)	0.40	1.00	1.00
- Yes	0	0 (13)		0	0

% (95% CI) 13 year incidence (95% confidence interval) of C3-C6 CVI

n = number of participants in reflux group at baseline with C3-C6 CVI at follow up, (N) = number in reflux group at baseline

*P value based on chi square test for difference in incidence of C3-C6 CVI by presence of reflux ≥ 0.5s in venous system at baseline

[a] Unadjusted odds ratio = crude odds ratio with no adjustments for age and sex

[b] Adjusted odds ratio = adjusted for age and sex

[1] Deep reflux = reflux ≥ 0.5s in CFV, FV origin, FV lower thigh, POP upper or POP lower and no reflux in GSV origin, GSV lower thigh or SSV

[2] Superficial reflux= reflux ≥ 0.5s in GSV origin, GSV lower thigh or SSV and no reflux in CFV, FV origin, FV lower thigh, POP upper or POP lower

[3] Combined reflux = reflux ≥ 0.5s in CFV, FV origin, FV lower thigh, POP upper or POP lower and reflux ≥ 0.5s in GSV origin, GSV lower thigh or SSV

TABLE 9.10 13 YEAR INCIDENCE OF C3-C6 CVI IN LEFT LEG AT FOLLOW UP BY PRESENCE OF REFLUX ≥ 0.5 SECONDS IN LEFT LEG AT BASELINE

	13 YEAR INCIDENCE C3-C6 CVI		P VALUE*	UNADJUSTED ODDS RATIO [a]	ADJUSTED ODDS RATIO [b]
REFLUX AT BASELINE	**% (95% CI)**	**n (N)**			
DEEP REFLUX [1]					
- No	8.7 (6.3-11.7)	41 (470)	0.50	1.00	1.00
- Yes	5.6 (1.8-13.4)	4 (72)		0.62 (0.21-1.77)	0.63 (0.21-1.87)
SUPERFICIAL REFLUX [2]					
- No	7.7 (5.4-10.6)	34 (442)	0.08	1.00	1.00
- Yes	15.8 (6.4-32.8)	6 (38)		2.25 (0.88-5.76)	1.92 (0.72-5.11)
DEEP + SUPERFICIAL [3]					
- No	8.4 (6.1-11.1)	44 (526)	0.51	1.00	1.00
- Yes	12.5 (0.6-61.6)	1 (8)		1.57 (0.19-13.01)	2.47 (0.27-22.47)

% (95% CI) 13 year incidence (95% confidence interval) of C3-C6 CVI

n = number of participants in reflux group at baseline with C3-C6 CVI at follow up, (N)= number in reflux group at baseline

*P value based on chi square test for difference in incidence of C3-C6 CVI by presence of reflux ≥ 0.5s in venous system at baseline

[a] Unadjusted odds ratio = crude odds ratio with no adjustments for age and sex

[b] Adjusted odds ratio = adjusted for age and sex

[1] Deep reflux = reflux ≥ 0.5s in CFV, FV origin, FV lower thigh, POP upper or POP lower and no reflux in GSV origin, GSV lower thigh or SSV

[2] Superficial reflux= reflux ≥ 0.5s in GSV origin, GSV lower thigh or SSV and no reflux in CFV, FV origin, FV lower thigh, POP upper or POP lower

[3] Combined reflux = reflux ≥ 0.5s in CFV, FV origin, FV lower thigh, POP upper or POP lower and reflux ≥ 0.5s in GSV origin, GSV lower thigh or SSV

TABLE 9.11 13 YEAR INCIDENCE OF C3-C6 IN RIGHT LEG BY PRESENCE OF REFLUX ≥ 0.5 SECONDS DURATION BY VEIN SEGMENT IN RIGHT LEG AT BASELINE

	13 YEAR INCIDENCE C3-C6 CVI		P VALUE*	UNADJUSTED ODDS RATIO [a]	ADJUSTED ODDS RATIO [b]
REFLUX AT BASELINE	**% (95% CI)**	**n (N)**			
CFV [1]					
- No	7.3 (5.2-9.9)	38 (519)	0.18	1.00	1.00
- Yes	0	0 (23)		0	0
FV [2]					
- No	6.6 (4.6-9.1)	34 (514)	0.12	1.00	1.00
- Yes	14.3 (4.5-35.4)	4 (28)		2.35 (0.77-7.17)	2.62 (0.81-8.49)
FV LOWER THIGH					
- No	6.9 (4.9-9.5)	36 (519)	0.49	1.00	1.00
- Yes	8.7 (1.4-28.7)	2 (23)		1.28 (0.29-5.67)	1.34 (0.29-6.25)
POP ABOVE KNEE [3]					
- No	7.0 (5.0-9.7)	35 (498)	0.63	0.97 (0.29-3.28)	1.00
- Yes	6.8 (1.7-18.5)	3 (44)		1.03 (0.28-3.75)	1.16 (0.33-4.05)
POP BELOW KNEE					
- No	6.9 (4.9-9.5)	34 (492)	0.47	1.00	1.00
- Yes	8.0 (2.5-19.3)	4 (50)		1.17 (0.40-3.45)	1.46 (0.48-4.44)

% (95% CI) 13 year incidence (95% confidence interval) of C3-C6 CVI

n = number of participants in reflux group at baseline with C3-C6 CVI up, N = number in reflux group at baseline

*P value based on chi square test for difference in incidence of C3-C6 CVI by presence of reflux ≥ 0.5s in vein segment at baseline

[a] Unadjusted odds ratio = crude odds ratio with no adjustments for age and sex

[b] Adjusted odds ratio = adjusted for age and sex

[1] CFV = common femoral vein

[2] FV = femoral vein

[3] POP = popliteal vein

TABLE 9.11 13 YEAR INCIDENCE OF C3-C6 IN RIGHT LEG BY PRESENCE OF REFLUX ≥ 0.5 SECONDS DURATION BY VEIN SEGMENT IN RIGHT LEG AT BASELINE

	13 YEAR INCIDENCE C3-C6 CVI		P VALUE*	UNADJUSTED ODDS RATIO [a]	ADJUSTED ODDS RATIO [b]
REFLUX AT BASELINE	**% (95% CI)**	**n (N)**			
GSV ORIGIN [1]					
- No	6.7 (4.7-9.1)	35 (526)	0.39	1.00	1.00
- Yes	14.3 (0.7-70.4)	1 (7)		2.34 (0.27-19.96)	1.53 (0.17-13.47)
GSV THIGH					
- No	6.4 (4.4-8.9)	31 (486)	0.32	1.00	1.00
- Yes	10.0 (2.5-27.2)	3 (30)		1.63 (0.47-5.68)	1.37 (0.38-4.94)
SSV THIGH [2]					
- No	7.2 (5.0-10.0)	33 (457)	0.50	1.00	1.00
- Yes	11.1 (0.6-54.8)	1 (9)		1.61 (0.19-13.23)	0.87 (0.10-7.59)

% (95% CI) 13 year incidence (95% confidence interval) of C3-C6 CVI
n = number of participants in reflux group at baseline with C3-C6 CVI at follow up, (N) = number in reflux group at baseline
*P value based on chi square test for difference in incidence of C3-C6 CVI by presence of reflux ≥ 0.5s in vein segment at baseline
[a] Unadjusted odds ratio = crude odds ratio with no adjustments for age and sex
[b] Adjusted odds ratio = adjusted for age and sex
[1] GSV = great saphenous vein
[2] SSV = short saphenous vein

TABLE 9.12 13 YEAR INCIDENCE OF C3-C6 IN LEFT LEG BY PRESENCE OF REFLUX ≥ 0.5 SECONDS DURATION BY VEIN SEGMENT IN LEFT LEG AT BASELINE

	13 YEAR INCIDENCE C3-C6 CVI		P VALUE*	UNADJUSTED ODDS RATIO [a]	ADJUSTED ODDS RATIO [b]
REFLUX AT BASELINE	**% (95% CI)**	**n (N)**			
CFV [1]					
- No	8.4 (6.2-11.2)	44 (521)	0.47	1.00	1.00
- Yes	4.8 (0.2-23.4)	1 (21)		0.54 (0.07-4.13)	0.56 (0.07-4.42)
FV [2]					
- No	8.1 (6.0-10.8)	43 (529)	0.29	1.00	1.00
- Yes	15.4 (2.6-50.8)	2 (13)		2.06 (0.44-9.57)	1.61 (0.33-7.95)
FV LOWER THIGH					
- No	8.4 (6.2-11.2)	44 (522)	0.49	1.00	1.00
- Yes	5.0 (0.3-24.6)	1 920)		0.57 (0.08-4.37)	0.71 (0.09-5.67)
POP ABOVE KNEE [3]					
- No	8.0 (5.8-10.7)	40 (502)	0.23	1.00	1.00
- Yes	12.5 (4.6-27.7)	5 (40)		1.65 (0.61-4.45)	2.04 (0.72-5.80)
POP BELOW KNEE					
- No	8.1 (5.9-10.9)	41 (505)	0.37	1.00	1.00
- Yes	10.8 (3.4-26.1)	4 (37)		1.37 (0.46-4.06)	1.85 (0.59-5.85)

% (95% CI) 13 year incidence (95% confidence interval) of C3-C6 CVI

n = number of participants in reflux group at baseline with C3-C6 CVI up, N = number in reflux group at baseline

*P value based on chi square test for difference in incidence of C3-C6 CVI by presence of reflux ≥ 0.5s in vein segment at baseline

[a] Unadjusted odds ratio = crude odds ratio with no adjustments for age and sex

[b] Adjusted odds ratio = adjusted for age and sex

[1] CFV = common femoral vein

[2] FV = femoral vein

[3] POP = popliteal vein

TABLE 9.12 13 YEAR INCIDENCE OF C3-C6 IN LEFT LEG BY PRESENCE OF REFLUX ≥ 0.5 SECONDS DURATION BY VEIN SEGMENT IN LEFT LEG AT BASELINE

	13 YEAR INCIDENCE C3-C6 CVI		P VALUE*	UNADJUSTED ODDS RATIO [a]	ADJUSTED ODDS RATIO [b]
REFLUX AT BASELINE	**% (95% CI)**	**n (N)**			
GSV ORIGIN [1]					
- No	7.5 (5.4-10.2)	39 (518)	0.08	1.00	1.00
- Yes	31.3 (11.4-69.2)	5 (16)		5.58 (1.85-16.88)	5.22 (1.62-16.81)
GSV THIGH					
- No	7.5 (5.7-10.7)	37 (491)	0.08	1.00	1.00
- Yes	15.4 (6.2-32.0)	6 (39)		2.24 (0.88-5.68)	2.08 (0.79-5.48)
SSV THIGH [2]					
- No	8.8 (6.4-11.8)	41 (466)	0.53	1.00	1.00
- Yes	0	0 (7)		0	0

% (95% CI) 13 year incidence (95% confidence interval) of C3-C6 CVI
n = number of participants in reflux group at baseline with C3-C6 CVI at follow up, (N) = number in reflux group at baseline
*P value based on chi square test for difference in incidence of C3-C6 CVI by presence of reflux ≥ 0.5s in vein segment at baseline
[a] Unadjusted odds ratio = crude odds ratio with no adjustments for age and sex
[b] Adjusted odds ratio = adjusted for age and sex
[1] GSV = great saphenous vein
[2] SSV = short saphenous vein

CHAPTER 10: RISK FACTORS AND INCIDENCE OF C2 VARICES AND C3-C6 CVI

10.1 CHAPTER OUTLINE

This chapter presents results of the univariate analysis on the association of various risk factors and the incidence of C2 varicose veins and C3-C6 CVI. Risk factors measured in the Edinburgh Vein Study include body mass index (BMI), family history of venous disease, medical history of venous conditions, pregnancy, oestrogen use including oral contraceptives and hormone replacement therapy (HRT), smoking, mobility at work, bowel habit and physical activity.

The incidence of C2 varices is the proportion of cases who developed new C2 varices at follow up in those initially free from C2 varices at baseline. The incidence of C3-C6 CVI is the proportion of new cases of C3-C6 CVI at follow up in those initially free from C2 varices and C3-C6 CVI at baseline. Therefore participants with C2 varicose veins at baseline whose symptoms worsened to C3-C6 CVI at follow up are not included as incident cases as they have not developed new disease but rather their existing venous disease has progressed. Also, it is important to consider that some new cases of C2 varicose veins or C3-C6 CVI may not have been identified as surgery after the initial examination may have eradicated signs of venous disease. Of the 555 participants free from C2-C6 disease at baseline, only 2 had surgery between the two stages of the study. However, despite treatment, both of these participants had C2 varicose veins at the follow up examination and therefore already included as incident cases.

The 13 year incidences of C2 varices and C3-C6 CVI are presented separately according to risk factor at baseline, with adjustments made for age and sex where appropriate. Changes in risk factors during follow up are also tested for their association with the incidence of these conditions. Bowel habit was measured at baseline only while physical activity was measured only at follow up. For these two risk factors, data is presented but changes during the follow up period cannot be measured.

Any risk factor found to be significant for the development of either C2 varices or C3-C6 CVI was entered with significant reflux results (presented in chapter 9) into a multivariate analysis to determine those factors that remained independently associated with incidence of either condition. The results of the multivariate analysis are presented at the end of this chapter.

10.2 BODY MASS INDEX

10.2.1 Baseline and follow up

The mean (SD) BMI of participants increased from 25.6 (4.4) kg/m^2 at baseline to 27.5 (4.8) kg/m^2 at follow up ($p<0.001$). Figure 10.1 displays the BMI category of participants at both stages of the study, based on the World Health Organisation classification. Few participants were classified as being underweight. The proportion of participants classified as a normal weight decreased from 49.0% to 30.1%, while the proportion classified as overweight increased from 36.7% at baseline to 44.5% at follow up. Moreover, the number of participants who were classified almost doubled from 12.9% at baseline to 24.6% at follow up.

Change in BMI was assessed by comparing BMI groups at baseline and follow up. Of the 870 participants with BMI measurements at both baseline and follow up, 520 (59.8%) participants stayed within the same BMI category; 4 (0.5%) underweight, 229 (26.3%) normal weight, 193 (22.2%) overweight and 94 (10.8%) obese. A total of 308 (35.4%) participants increased by one or more BMI categories: 9 (1.0%) participants went from being underweight at baseline to a normal weight at follow up, 179 (20.6%) went from being a normal weight to overweight, 16 (1.8%) went from being a normal weight to obese and 104 (12.0%) went from being overweight to obese. A total of 42 (4.8%) participants decreased by one or more BMI categories; 3 (0.3%) went from a normal weight at baseline to underweight at follow up, 22 (2.6%) went from overweight to a normal weight, 2 (0.2%) went from obese to a normal weight and 15 (1.7%) went from obese to overweight.

10.2.2 Incidence of C2 varicose veins

To examine the association between BMI and incidence of C2 varicose veins, 555 participants free of varices at baseline were selected. Of these, 8 (1.4%) were underweight at baseline, 278 (50.1%) normal weight, 196 (35.3%) overweight and 73 (13.2%) obese. Table 10.1 shows that the incidence of C2 varices at follow up was 25% (95% CI 4.2-82.6), 16.5% (95% CI 12.3-21.9), 19.4% (95% CI 13.9-26.3) and 20.5% (95% CI 11.9-33.1) in participants who were underweight, normal weight, overweight and obese at baseline respectively (p trend=0.43). There were no significant differences in the incidence according to change in BMI from baseline to follow up. The 13-year incidence was 17.9% (95% CI 13.7-33.1) in participants who stayed in the same BMI group, 16.9% (95% CI 12.0-23.2) in those whose BMI group increased, and 26.1% (95% CI 10.6-54.3) in those whose BMI group decreased from baseline to follow up (p trend=0.55).

10.2.3 Incidence of C3-C6 chronic venous insufficiency

Of 546 participants free of CVI at baseline, 8 (1.5%) were underweight, 277 (50.7%) were normal weight, 189 (34.6%) were overweight and 72 (13.2%) were obese. None of the participants who were underweight at baseline developed CVI. Increased BMI at baseline was significantly associated with development of C3-C6 CVI at follow up ($p<0.001$) [Table 10.2]. This association remained significant after adjusting for age and sex. Participants who were overweight at baseline were 1.3 (95% CI 1.1-1.6) times more likely to have C3-C6 CVI at follow up. In obese participants, the odds were even higher at 4.5 (95% CI 3.3-6.9). Change in BMI was not associated with the development of C3-C6 CVI. The 13-year incidence was 10.1% (95% CI 7.0-14.1), 7.5% (95% CI 4.4-12.1), and 13.0% (95% CI3.3-35.5) in those whose BMI group stayed the same, increased and decreased from baseline to follow up (p trend=0.55).

10.3 FAMILY HISTORY

10.3.1 Baseline and follow up

At baseline, 392 (45.6%) out of 860 participants reported a positive maternal or paternal family history of chronic venous disease (CVD) In those 392 participants, 62.2% had a maternal family history, 22.5% had a paternal family history and 15.3% had a history in both parents. At follow up, 373 (43.9%) of 852 participants reported a family history, 60.9% in the mother only, 22.5% in the father only and 16.6% in both parents.

10.3.2 Incidence of C2 varicose veins

Family history of CVD in either first-degree relative was associated with incidence of C2 varicose veins [Table 10.3]. The 13-year incidence was 23.3% (95% CI 17.5-30.4) and 14.8% (95% CI 11.0-19.5) in those with and without a family history respectively (p=0.09). After adjusting for age and sex, those with a family history in either parent were 1.7 (95% CI 1.1-2.7) times more likely to develop C2 varices at follow up. Participants with a maternal history had a significantly higher incidence (23.2%, 95% CI 16.6-31.5) than those with no maternal history (15.7%, 95% CI 12.1-20.1) (p=0.04) and this remained significant after adjusting for age and sex (OR 1.6, 95% CI 1.0-2.6). Paternal family history was not associated with the incidence of C2 varices (p=0.20). Fewer participants reported a paternal family history (n=88) and this small sample may have contributed to the lack of a significant association. Changes in family history from baseline to follow up and incidence of C2 varices was not analysed due to the fact that this is relatively constant, as reflected in the equal proportions of participants reporting this at baseline and follow up (45.6% and 43.9% respectively).

10.3.3 Incidence of C3-C6 chronic venous insufficiency

Table 10.4 shows that family history of CVD was not a significant risk factor for the incidence of C3-C6 CVI. Among participants with no family history, the incidence of C3-C6 CVI was 8.2% (95% CI 5.4-11.8) compared to 10.7% (95% CI 6.9-15.8) in participants with a history of CVD in either mother or father (p=0.40). When analysed separately, neither maternal (p=0.20) nor paternal (p=0.80) family history were associated with the development of C3-C6 CVI.

10.4 MEDICAL HISTORY

10.4.1 Baseline and follow up

In the questionnaires at both baseline and follow up, participants were asked to report previous medical history of conditions which have been linked to CVD. These include deep vein thrombosis (DVT), phlebitis, swollen leg (post-operatively, post-pregnancy or other), fractured leg, inguinal hernia and pulmonary embolism. Certain conditions such as white leg of pregnancy and arthritis were measured at follow up only. Data on the prevalence of these conditions at baseline and follow up are shown in Table 10.5. The number of participants affected by conditions such as DVT, phlebitis, hernia and pulmonary embolism were small. From baseline to follow up, there was a slight increase in the prevalence of these conditions, although the increase was not statistically significant. The number of participants reporting a swollen leg post pregnancy decreased from 35.4% at baseline to just 7.8% at follow up. The same was true for swollen legs caused by other reasons, with 21.9% of participants reporting a history of this condition at baseline compared to just 1.8% at follow up. Almost a third (32.2%) of participants at baseline reported having haemorrhoids.

10.4.2 Incidence of C2 varicose veins

The 13-year incidence of C2 varicose veins by medical history at baseline is shown in Table 10.6. History of DVT was significantly associated with increased incidence of C2 varices (p=0.02). The incidence was 17.6% (95% CI 14.4-21.4) in those with no DVT compared to 50.0% (95% CI 18.3-110.8) in those with a previous DVT (p=0.02). However this association was not significant after adjusting for age (OR 3.5, 95% CI 1.0-12.4). It should be noted that only 10 participants had a DVT at baseline, 5 of whom

went on to develop C2 varices. For phlebitis, the incidence was 42.9% (95% CI 17.4-89.1) compared to 17.4% (95% CI 14.2-21.2) in participants with and without this condition respectively (p=0.03). Again this association diminished after adjusting for age and sex (OR 2.8, 95% CI 0.9-8.4). Other medical conditions such as swollen leg, fractured leg, hernia, haemorrhoids and pulmonary embolism, were not associated with incidence of C2 varicose veins (all p≥0.05).

10.4.3 Incidence of C3-C6 chronic venous insufficiency

Table 10.7 presents the 13-year incidence of C3-C6 CVI by history of medical conditions at baseline. The incidence of CVI was significantly higher in those with an inguinal hernia (26.7%, 95% CI 12.4-50.6) compared to those with no history of this condition (8.2%, 95% CI 5.9-10.9) (p=0.001). After adjusting for age and sex, participants with a history of inguinal hernia at baseline were over 3 times more likely to develop C3-C6 CVI at follow up (OR 3.1, 95% CI 1.3-7.8). Other medical conditions such as history of DVT, phlebitis, haemorrhoids, swollen or fractured leg and pulmonary embolism were not significantly associated with the incidence of C3-C6 CVI at follow up (all p≥0.05).

10.5 PREGNANCY

10.5.1 Baseline and follow up

Data on pregnancy was collected via the study questionnaire. At baseline, 23.5% of the 490 female participants had never been pregnant, 40.6% had been pregnant 1-2 times, 21.8% had been pregnant 3 times and 14.1% had been at least 4 times. At follow up, the proportion of participants who had been pregnant 1-2 times, 3 times and ≥4 times, increased to 42.9%, 25.5% and 16.6% respectively (Figure 10.2]

10.5.2 Incidence of C2 varicose veins

Table 10.8 displays the 13-year incidence of C2 varicose veins by number of pregnancies at baseline. The incidence of C2 varicose veins in those never pregnant (n=90) was 16.7% (95% CI 9.7-26.9), 16.3% (95% CI 10.5-24.3) in those with 1-2 pregnancies (n=135), 20.0% (95% CI 11.1-33.3) in those with 3 pregnancies (n=65) and highest in those with ≥4 pregnancies (n=44) with an incidence of 27.3% (95% CI 14.8-46.4) (p trend=0.14). Change in the number of pregnancies from baseline to follow up and the association with incidence of C2 varicose veins was measured. A total of 307 women were free of varicose veins at baseline and had complete pregnancy data at both stages of the study. The 13-year incidence of varicose veins was 20.7% (95% CI 15.6-27.0) in those with no further pregnancies, 13.3% (95% CI 4.2-32.2) with one further pregnancy, 7.1% (95% CI 0.4-35.2) with 2 further pregnancies and 22.2% (95% CI 3.7-73.4) in those who had 3 further pregnancies between the baseline and follow up phases of the study. However the numbers are very small with only 7 women in total experiencing one or more pregnancies during the follow up period of the study.

10.5.3 Incidence of C3-C6 chronic venous insufficiency

Of the 331 female participants free of CVI at baseline, 89 (26.9%) had never been pregnant, 134 (40.5%) had been pregnant 1-2 times, 65 (19.6%) had been pregnant 3 times and 43 (13.0%) had been pregnant at least 4 times. The 13-year incidence of C3-C6 CVI by number of pregnancies at baseline is shown in Table 10.9. There was no association between number of pregnancies and incidence of CVI. The incidence was 5.6% (95% CI 2.1-12.4) in those never pregnant, 9.0% (95% CI 4.8-15.2) in those pregnant 1-2 times, 9.2% (95% CI 3.7-19.2) in those who had been pregnant 3 times and 9.3% (95% CI 3.0-22.4) in those who had been pregnant at least 4 times (p=0.42).

Pregnancy during the follow up period of the study was not associated with incidence of CVI. The incidence of CVI in female participants who had not been pregnant between baseline and follow up was 8.5% (95% CI 5.4-12.7), 3.3% (95% CI 0.2-16.4) in those who had had one further pregnancy, and 11.1% (95% CI 0.6-54.8) in those who had been pregnant three times between baseline and follow up (p=0.88).

10.6 ORAL CONTRACEPTIVE

10.6.1 Baseline and follow up

The proportion of oral contraceptive users was similar at both stages of the study: 73.3% and 75.3% ever having used oral contraceptives at baseline and follow up respectively. Of the 354 users at baseline, 57 (16.1%) were current users while the remaining 297 (83.9%) used oral contraceptives before taking part in the baseline study. Of the 354 users at follow up, 19 (5.4%) were current users while the remaining 335 (94.6%) had taken oral contraceptives before the follow up.

10.6.2 Incidence of C2 varicose veins

Incidence of C2 varicose veins was not associated with oral contraceptive use at baseline (p=0.50). The 13-year incidence of C2 varices was 22.2% (95% CI 13.2-35.3) in female participants who had never used oral contraceptives (n=72) compared to 17.4% (95% CI 12.9-23.1) in participants who had ever used oral contraceptives (n=258). The age-adjusted odds ratio was 1.2 (95% CI 0.6-2.5).

10.6.3 Incidence of C3-C6 chronic venous insufficiency

Women who had never been on oral contraceptives appeared to be more likely to develop C3-C6 CVI at follow (p=0.001). The 13 year incidence of CVI was 18.1% (95% CI 10.0-30.1) in women who had never been on oral contraceptives (n=72) compared to just 5.5% (95% CI 3.1-9.0) in women who had previously used oral contraceptives (n=255). However, after adjusting for age, this association was no longer significant (OR 0.5, 95% CI 0.2-1.2).

10.7 HORMONE REPLACEMENT THERAPY

10.7.1 Baseline and follow up

At baseline, 95 out of 486 (19.3%) female participants had ever been on HRT. At follow up the proportion of HRT users increased to 33.0% (155 out of 470) Of the 95 HRT users at baseline, 58 (61.1%) were using HRT at that time and the remaining 37 (38.9%) used HRT prior to the baseline study. Among 155 HRT users at follow up, 18 (11.6%) were taking HRT during the study while the remaining 137 (88.4%) were on HRT before taking part in the follow up study.

10.7.2 Incidence of C2 varicose veins

HRT use was associated with an increased incidence of C2 varicose veins (p=0.03). The 13-year incidence of varicose veins was 16.5% (95% CI 12.2-21.9) in female participants who had never been on HRT (n=273) compared to 29.8% (95% CI 18.0-46.8) in HRT users (n=57). After adjustments were made for age, the association was no longer significant. The odds ratio for developing C2 varices was 1.5 (95% CI 0.7-3.0) in women who had used HRT at baseline.

10.7.3 Incidence of C3-C6 chronic venous insufficiency

The incidence of C3-C6 CVI was similar in women regardless of previous HRT use (P=0.50). The incidence was 8.5% (95% CI 5.5-12.5) in women who had never used HRT (n=271) compared to 7.1% (95% CI 2.3-17.2) in previous HRT users (n=56) (p=0.50). After adjusting for age, the odds of developing C3-C6 CVI with previous HRT use were 0.4 (95% CI 0.1-1.3).

10.8 MOBILITY AT WORK

10.8.1 Baseline and follow up

Mobility at work was split into four categories at baseline: sitting, standing, walking and lifting heavy objects at work. The responses were merged to form two categories so that for each type of activity at work, the response was less than 50% of the time at work and more than 50% of the time spent at work. Of the 880 participants at baseline, 389 (44.2%) spent more than 50% of their day at work sitting, 262 (29.8%) standing, 242 (27.5%) walking whilst 109 (12.4%) spent more than 50% of their working day lifting heavy objects.

At follow up, the questionnaire was adapted slightly from that administered at baseline. Participants were asked to answer which one of the four activities from sitting, standing, walking and lifting heavy objects, best reflected their working day. Of the 848 participants with completed data for this risk factor, 254 (30.0%) reported that they sat at work most of the day, 474 (55.9%) stood, 100 (11.8%) walked at work whilst the remaining 20 (2.4%) worked in jobs where they were required to lift heavy objects.

10.8.2 Incidence of C2 varicose veins

The 13-year incidence of C2 varicose veins by mobility at work at baseline is displayed in Table 10.10. There were no significant associations between type of work and incidence of varicose veins at follow up (all p≥0.05). The age-and sex-adjusted odds ratios of developing C2 varices in those who spent > 50% of their working day sitting, standing, walking or heavy lifting were 0.9 (95% CI 0.6-1.5), 1.0 (95% CI 0.6-1.6), 0.9 (95% CI 0.6-1.6) and 1.3 (95% CI 0.7-2.4) respectively.

10.8.3 Incidence of C3-C6 chronic venous insufficiency

Table 10.11 shows the 13-year incidence of C3-C6 CVI by type of work at baseline. Like C2 varicose veins, there was no significant association between type of work at baseline and incidence of CVI at follow up (all p≥0.05). In participants who were sedentary at work and sat for more than 50% of the time, the 13-year incidence of C3-C6 CVI was 7.6% (95% CI 4.7-11.7). The incidence of C3-C6 CVI in participants who stood, walked and did heavy work was 9.0% (95% CI 5.0-14.9), 10.6% (95% CI 6.1-17.0) and 10.4% (95% CI 4.6-20.7) respectively.

10.9 SMOKING

10.9.1 Baseline and follow up

Figure 10.3 shows the smoking status of participants at the baseline and follow up stages of the study. At baseline, of the 877 participants with complete data on smoking, 465 (53.0%) had never smoked, 228 (26.0%) were ex-smokers and 184 (21.0%) were current smokers. Of the 184 current smokers, 168 (91.3%) smoked cigarettes whilst 16 (8.7%) smoked cigars or pipes. At follow up, smoking data was available for 847 participants. Of these, 478 (56.4%) reported to never have smoked, 264 (31.2%) had previously smoked but had since stopped and 105 (12.4%) were current smokers. Of the 105 current smokers, 99 (94.3%) smoked cigarettes whilst 6 (5.7%) smoked cigars or pipes. When analysing changes in smoking status from baseline to follow up 844 participants had complete smoking data for both stages of the study. Of the 454 participants who had never smoked at baseline, 2 were current smokers and 7 were ex-smokers at follow up. Of the 172 smokers at baseline, 96 were still smoking at follow up whilst 64 had since given up smoking. Of the 218 ex-smokers at baseline, 193 were still ex-smokers whilst 7 had started smoking again at follow up.

10.9.2 Incidence of C2 varicose veins

Smoking was not significantly associated with increased incidence of C2 varicose veins (p trend=0.93). The 13-year incidence was 18.8% (95% CI 14.3-24.3) in non-smokers (55 out of 292), 17.5% (95% CI 11.6-25.4) in ex-smokers (25 out of 143) and 17.8% (95% CI 11.3-26.7) in those who smoked at baseline (21 out of 118). The age- and sex-adjusted odds ratios were 1.0 (95% CI 0.6-1.7) for ex-smokers and 0.9 (95% CI 0.5-1.5) for current smokers.

10.9.3 Incidence of C3-C6 chronic venous insufficiency

There was no significant association between smoking and the development of C3-C6 CVI at follow up (p trend=0.82). The incidence of CVI was 9.3% (95% CI 6.3-13.4%) in non-smokers (27 out of 290), 8.5% (95% CI 4.6-14.5) in ex-smokers (12 out of 141) and 9.7% (95% CI 5.1-16.9%) in current smokers (11 out of 113). The age-and sex adjusted odds ratios were 1.2 (95% CI 0.6-2.6) and 1.8 (95% CI 0.4-1.7) in ex-smokers and smokers respectively.

10.10 BOWEL HABIT

10.10.1 Baseline

Bowel habit was recorded at the baseline phase of the study only. Participants were asked, on average, how many days per week they opened their bowels and how many times per day. Among 879 participants at baseline, the mean (SD) number of days per week they opened their bowels was 6.2 (1.4) and the mean (SD) number of times per day was 1.3 (0.6). Participants were also asked if they had to strain to start and finish a bowel movement, with the option of two responses, "only occasionally" or "half of the time or nearly always". Seven hundred and fifty six (86.0%) participants occasionally had to strain to start a bowel movement compared to 123 (14.0%) who had to strain half of the time. To finish a bowel movement, 795 (90.8%) only occasionally had to strain while 81 (9.2%) had to strain half of the time.

10.10.2 Incidence of C2 varicose veins

There was no significant association between straining to start a bowel movement and the incidence of C2 varices. The incidence was 18.0% (95% CI 14.4-22.1) in participants who occasionally strained to start a bowel movement and 18.5% (95% CI 10.6-30.6) in those who strained half of the time (p=0.88). The-age and sex-adjusted odds ratio was 1.0 (95% CI 0.5-1.9). Straining to finish a bowel movement was not associated with C2 varices. The incidence was 18.4% (95% CI 14.9-22.5) in participants who occasionally strained to finish compared to 15.5% (95% CI 7.6-28.5) in participants who strained to finish a bowel movement half of the time (p=0.59). The age- and sex-adjusted odds ratio was 0.7 (95% CI 0.3-1.5).

Frequency of bowel movements was also compared. On average, the mean (SD) number of bowel movements was 6.2 (SD) days per week in those with no varicose veins compared to 6.1 (1.5) in participants with varicose veins (p=0.71). Bowel movements per day were also similar in the two groups: mean (SD) 1.3 (0.6) and 1.3 (0.5) in those with and without varicose veins respectively (p=0.3).

10.10.3 Incidence of C3-C6 chronic venous insufficiency

Like C2 varicose veins, bowel habit had no significant effect on the development of C3-C6 CVI at follow up. The 13-year incidence of CVI in those who occasionally strained to start a bowel movement was 9.1% (95% CI 6.7-12.2) compared to 9.3% (95% CI 4.1-18.5) in those who strained half of the time (p=0.96). The incidence was 9.3% (95% CI 6.8-12.3) in those who occasionally strained to finished compared to 8.6% (95% CI 3.1-19.1) in those who strained to finish half of the time (p=0.87).

The frequencies of bowel movements were compared in participants with and without CVI at follow up. The mean (SD) number of days per week the bowels moved was 6.1 (1.5) in participants with no CVI at follow up compared to 6.2 (1.3) in those with CVI at follow up (P=0.8). There was no difference between number of times per day the bowels moved, with a mean (SD) of 1.3 (0.5) times per day in those with no CVI and 1.4 (0.7) times per day in those with CVI at follow up (p=0.2).

10.11 PHYSICAL ACTIVITY

10.11.1 Follow up

Physical activity was measured in the follow up questionnaire only. Participants were given examples of light, moderate and strenuous activity and asked to report how many times a week they participated in each activity during summer and winter. Light activity included walking, gardening, light DIY and yoga. Moderate activity included badminton, cycling, golf, jogging, swimming and tennis while strenuous activity included competitive running, field sports, sports training and squash. On average, the mean (SD) number of times participants performed light activities was 6.5 (6.7) times a week. For moderate and strenuous activity, the mean (SD) was 2.3 (4.0) and 0.4 (1.4) respectively. A more detailed summary is provided in Figure 10.4, which shows the mean number of times per week each activity was performed in summer and winter. Light and moderate physical activities were performed more often in summer than in winter whilst there was no difference in strenuous activity.

10.11.2 Prevalence of C2 varicose veins

Of the 555 participants free of varicose veins at baseline, physical activity data was available for 533 at follow up For 435 participants with no C2 varices at follow up, the mean (SD) number of times they took part in light activity was 6.4 (6.5) compared to 6.0 (6.9) in 98 participants with new trunk varicose veins at follow up (p=0.53). Moderate activity was completed a mean of 2.1 (3.1) and 2.3 (3.7) times per week in those with and without C2 varices respectively (p=0.54). Participants who did not have varicose veins were more likely to participate in strenuous physical activity (p<0.001). At follow up, strenuous physical activity was performed 0.4 (1.3) times per week in 434 participants with no trunk varicose veins compared to 0.2 (0.7) times per week in 98 participants with varicose veins at follow up. It is worth noting these results are merely measuring the level of physical activity in those with and without C2 varicose veins at follow up. Associations between physical activity and incidence of varicose veins cannot be determined because baseline data on levels of physical activity are not available.

10.11.3 Prevalence of C3-C6 chronic venous insufficiency

Participants with CVI exercised less than those with no CVI (p=0.007). In 477 participants with no CVI at follow up, the mean (SD) number of times they took part in light activity was 6.3 (6.3) compared to 6.6 (8.8) in 47 participants with CVI at follow up (p=0.8). The mean (SD) number of times per week moderate activity was undertaken was 2.2 (3.2) in those with no CVI compared to 1.9 (3.9) in those with CVI at follow up (p=0.6). At follow up, strenuous physical activity was performed 0.4 (1.3) times per week in participants with no CVI compared to 0.1 (0.2) times per week in those with CVI at follow up.

10.12 MULTIVARIATE ANALYSIS

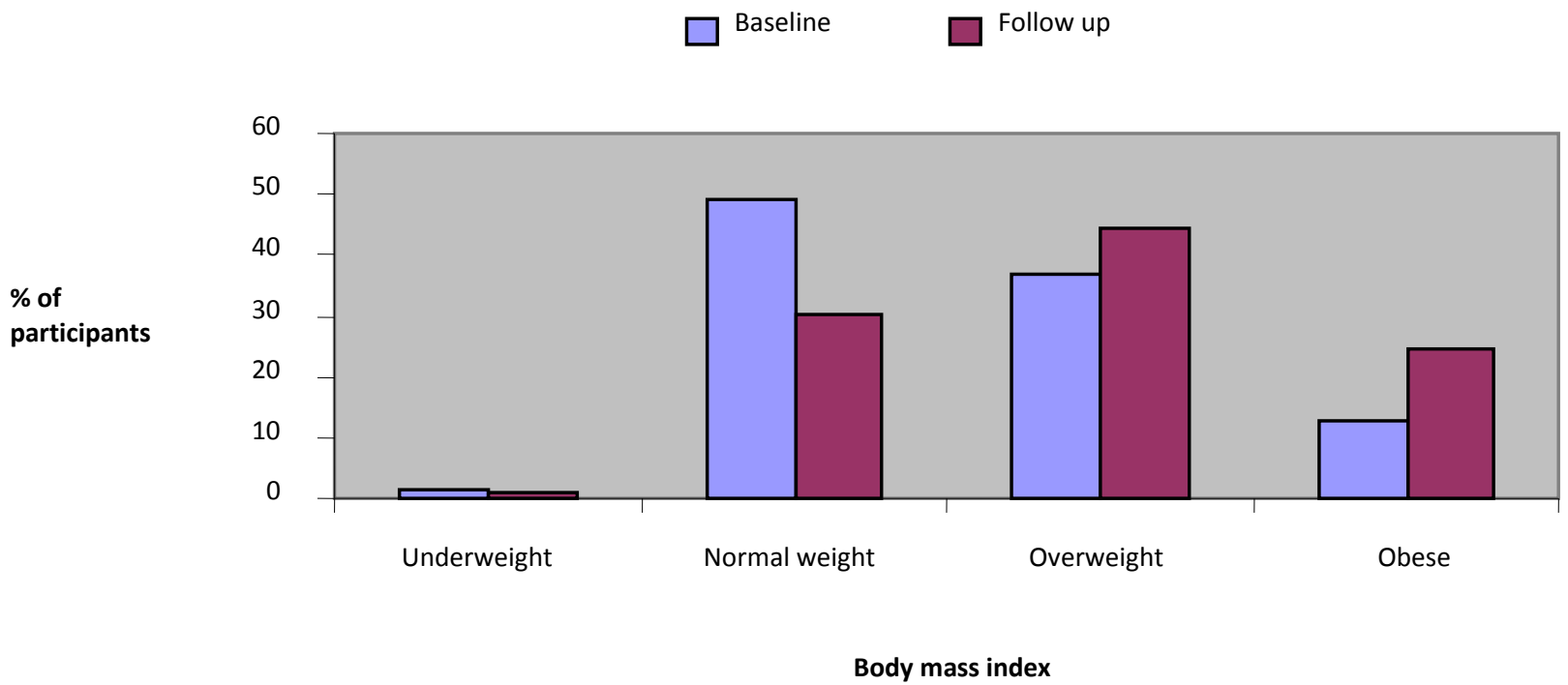
Univariate analysis on the association of reflux ≥ 0.5 seconds at baseline with new C2 varices at follow up determined that reflux in the superficial veins alone or accompanied by reflux in the deep veins, was significant in the development of C2 varices (Chapter 9). Univariate analysis in this chapter has shown that family history of CVD was the only risk factor significantly associated with the incidence of C2 varicose veins. These three factors were entered into a logistic regression model with adjustments for age and sex. Results showed that superficial reflux only (OR 2.97, 95% CI 1.52-5.81), combined reflux (OR 4.24, 95% CI 1.92-9.37) and family history of CVD (OR 1.73, 95% CI 1.04-2.88) at baseline all remained significantly associated with the incidence of C2 varicose veins at follow up.

Reflux at baseline was not significantly associated with the incidence of C3-C6 CVI at follow up. However, two risk factors showed a significant association on univariate analysis: obesity and inguinal hernia. These two factors were entered into a logistic regression model with age and sex. Both inguinal hernia and obesity remained significant risk factors for the incidence of C3-C6 CVI with adjusted odds ratios of 3.6 (95% CI 1.4-9.1) and 4.4 (95% CI 1.4-7.5) respectively.

10.13 CHAPTER SUMMARY

This study examined risk factors measured at baseline and measured their association with the development of C2 varicose veins and C3-C6 chronic venous insufficiency at follow up. Family history, in particular maternal family history of chronic venous disease, was significantly associated with the incidence of C2 varicose veins. However, it was not associated with the development of C3-C6 CVI. On the other hand, obesity was a significant risk factor for the development of C3-C6 CVI but not for C2 varicose veins. Participants classified as obese at baseline were almost four times more likely to develop CVI at follow up than those of a normal weight. The incidence of C2 varicose veins appeared to increase with number of pregnancies. Although this trend was not significant, the lack of statistical association must be interpreted with caution due to the small numbers in this study. History of DVT and phlebitis were associated with incidence of C2 varicose veins, although these associations reduced and became non-significant after adjusting for age and sex. Moreover, those with an inguinal hernia at baseline were more likely to develop C3-C6 CVI at follow up. However, caution must be exercised in interpreting these results on history of medical conditions as the number of participants with these conditions was probably too small to estimate the incidence of CVD with precision. Smoking, mobility at work and bowel habits at baseline showed no association with the incidence of C2 varicose veins or C3-C6 CVI at follow up.

FIGURE 10.1 BODY MASS INDEX AT BASELINE AND FOLLOW UP



Underweight = BMI <18.50 kg/m^2, normal weight = BMI 18.50-24.99 kg/m^2, overweight = BMI 25.00-29.99 kg/m^2, obese = BMI ≥ 30 kg/m^2

TABLE 10.1 13 YEAR INCIDENCE OF C2 VARICOSE VEINS AT FOLLOW UP ACCORDING TO BODY MASS INDEX (BMI) AT BASELINE AND SUBSEQUENT CHANGES TO BMI DURING FOLLOW UP

	13 YEAR INCIDENCE C2 VARICOSE VEINS		P TREND *	UNADJUSTED OR [a]	ADJUSTED OR [b]
BODY MASS INDEX (BMI)	**% (95% CI)**	**n (N)**		**(95% CI)**	**(95% CI)**
BMI GROUP AT BASELINE [c]					
Underweight	25.0 (4.2-82.6)	2 (8)	0.43	1.60 (0.12-3.04)	1.66 (0.13-3.46)
Normal weight	16.5 (12.3-21.9)	46 (278)		1.00	1.00
Overweight	19.4 (13.9-26.3)	38 (196)		1.72 (0.14-3.71)	1.69 (0.13-3.62)
Obese	20.5 (11.9-33.1)	15 (73)		1.78 (0.14-4.23)	1.69 (0.12-3.84)
CHANGE BASELINE TO FOLLOW UP [d]					
BMI group stayed the same	17.9 (13.7-23.0)	57 (318)		1.00	1.00
BMI group increased	16.9 (11.9-23.3)	35 (207)	0.80	0.93 (0.59-1.48)	1.02 (0.64-1.63)
BMI group decreased	26.1 (10.6-54.3)	6 (23)		1.62 (0.61-4.28)	1.20 (0.44-3.30)

n= number of participants in BMI group at baseline with C2 varices at follow up, (N) = number of participants in BMI group at baseline

* P value based on test for linear association between BMI and incidence of C2 varicose veins at follow up. p<0.05 denotes statistical significance

[a] Unadjusted odds ratio = crude odds ratio for the risk of developing C2 varicose veins, with no adjustment for age or sex

[b] Adjusted odds ratio = odds ratio for the risk of developing C2 varicose veins, adjusted for age and sex

[c] BMI group at baseline: underweight = BMI < 18.5 kg/m^2, normal weight = BMI 18.5-24.99 kg/m^2, overweight = BMI 25.0-29.99 kg/m^2, obese = BMI ≥ 30 kg/m^2 (WHO)

[d] Change in BMI group from baseline to follow up.

Incidence of C2 varicose veins based on the number of new cases of C2 varicose veins at follow up divided by the number of participants free from C2 varicose veins at baseline.

TABLE 10.2 13 YEAR INCIDENCE OF C3-C6 CHRONIC VENOUS INSUFFICIENCY AT FOLLOW UP ACCORDING TO BODY MASS INDEX (BMI) AT BASELINE AND SUBSEQUENT CHANGES TO BMI DURING FOLLOW UP

	13 YEAR INCIDENCE C3-C6 CVI		P TREND *	UNADJUSTED OR [a]	ADJUSTED OR [b]
BODY MASS INDEX (BMI)	**% (95% CI)**	**n (N)**		**(95% CI)**	**(95% CI)**
BMI GROUP AT BASELINE [c]					
Underweight	0.0	0 (8)	<0.001	-	-
Normal weight	6.1 (3.7-9.6)	17 (277)		1.00	1.00
Overweight	8.5 (5.0-13.4)	16 (189)		1.49 (0.11-3.24)	1.33 (1.14-1.64)
Obese	23.6 (14.2-37.0)	17 (72)		4.99 (0.14-7.45)	4.49 (3.26-6.92)
CHANGE BASELINE TO FOLLOW UP [d]					
BMI group stayed the same	10.1 (7.0-14.1)	32 (316)	0.55	1.00	1.00
BMI group increased	7.5 (4.4-12.1)	15 (200)		0.72 (0.38-1.37)	0.87 (0.45-1.68)
BMI group decreased	13.0 (3.3-35.5)	3 (23)		1.33 (0.38-4.73)	0.93 (0.25-3.45)

n= number of participants in BMI group at baseline with C3-C6 CVI at follow up, (N) = number of participants in BMI group at baseline

* P value based on test for linear association between BMI and incidence of C3-C6 CVI at follow up $p<0.05$ denotes statistical significance

[a] Unadjusted odds ratio = crude odds ratio for the risk of developing C3-C6 CVI, no adjustment for age or sex

[b] Adjusted odds ratio = odds ratio for the risk of developing C3-C6 CVI, adjusted for age and sex

[c] BMI group at baseline: underweight = BMI < 18.5 kg/m^2, normal weight = BMI 18.5-24.99 kg/m^2, overweight = BMI 25.0-29.99 kg/m^2, obese = BMI ≥ 30 kg/m^2 (WHO)

[d] Change in BMI group from baseline to follow up.

Incidence of C3-C6 CVI based on the number of new cases of C3-C6 CVI at follow up, divided by the number of participants free from C2 varices and C3-C6 CVI at baseline.

TABLE 10.3 13 YEAR INCIDENCE OF C2 VARICOSE VEINS AT FOLLOW UP BY FAMILY HISTORY OF VENOUS DISEASE AT BASELINE

	13 YEAR INCIDENCE C2 VARICOSE VEINS		P VALUE *	UNADJUSTED OR [b]	ADJUSTED OR [c]
FAMILY HISTORY AT BASELINE [a]	% (95% CI)	n/N		(95% CI)	(95% CI)
ANY FH					
No	14.8 (11.0-19.5)	48 (324)	0.09	1.00	1.00
Yes	23.3 (17.5-30.4)	51 (219)		1.75 (1.13-2.71)	1.74 (1.11-2.71)
MATERNAL FH					
No	15.7 (12.1-20.1)	59 (375)	0.04	1.00	1.00
Yes	23.2 (16.6-31.5)	38 (164)		1.62 (1.02-2.55)	1.64 (1.03-2.61)
PATERNAL FH					
No	17.5 (13.9-21.8)	78 (445)	0.20	1.00	1.00
Yes	24.4 (15.1-37.3)	19 (78)		0.72 (0.38-1.37)	0.87 (0.45-1.68)

n= number of participants with family history at baseline and C2 varicose veins at follow up, (N)=number of participants with family history at baseline

* P value based on chi square test for association between family history of CVD at baseline and incidence of C2 varicose veins at follow up. $p<0.05$ denotes statistical significance

[a] Family history of C2-C6 chronic venous disease in either mother or father

[b] Unadjusted odds ratio = crude odds ratio for the risk of developing C2 varicose veins with no adjustment for age or sex

[c] Adjusted odds ratio = odds ratio for the risk of developing C2 varicose veins, adjusted for age and sex

Incidence of C2 varicose veins based on the number of new cases of C2 varicose veins at follow up divided by the number of participants free from C2 varicose veins at baseline.

TABLE 10.4 13 YEAR INCIDENCE OF C3-C6 CHRONIC VENOUS INSUFFICIENCY AT FOLLOW UP BY FAMILY HISTORY OF VENOUS DISEASE AT BASELINE

	13 YEAR INCIDENCE C3-C6 CVI		P VALUE *	UNADJUSTED OR [b]	ADJUSTED OR [c]
FAMILY HISTORY AT BASELINE [a]	% (95% CI)	n/N		(95% CI)	(95% CI)
ANY FH					
No	8.2 (5.4-11.8)	26/319	0.40	1.00	1.00
Yes	10.7 (6.9-15.8)	23/215		1.35 (0.75-2.43)	1.36 (0.74-2.49)
MATERNAL FH					
No	8.1 (5.6-11.4)	30/370	0.20	1.00	1.00
Yes	11.9 (7.4-18.2)	19/160		1.53 (0.83-2.80)	1.61 (0.86-3.01)
PATERNAL FH					
No	8.9 (6.4-12.0)	39/438	0.80	1.00	1.00
Yes	10.4 (4.8-19.7)	8/77		1.19 (0.53-2.65)	1.18 (0.52-2.68)

n= number of participants with family history at baseline and C3-C6 CVI at follow up, (N)=number of participants with family history at baseline

* P value based on chi square test for association between family history of CVD at baseline and incidence of C3-C6 CVI at follow up. $p<0.05$ denotes statistical significance

[a] Family history of C2-C6 chronic venous disease in either mother or father

[b] Unadjusted odds ratio = crude odds ratio for the risk of developing C3-C6 CVI with no adjustment for age or sex

[c] Adjusted odds ratio = odds ratio for the risk of developing C3-C6 CVI, adjusted for age and sex

Incidence of C3-C6 CVI based on the number of new cases of C3-C6 CVI at follow up, divided by the number of participants free from C2 varices and C3-C6 CVI at baseline.

TABLE 10.5 HISTORY OF MEDICAL CONDITIONS AT BASELINE AND FOLLOW UP

	BASELINE		FOLLOW UP		P VALUE
MEDICAL CONDITION AT BASELINE	%	n	%	n	
Deep vein thrombosis	2.5	22	3.4	29	0.32
Phlebitis	4.7	41	5.2	44	0.45
Swollen leg post operatively	6.3	53	4.6	39	<0.001
Swollen leg post pregnancy*	35.4	135	7.8	37	<0.001
Swollen leg other	21.9	165	1.8	15	<0.001
Broken leg	9.4	82	8.9	76	0.54
Hernia	6.0	53	6.9	59	0.48
Haemorrhoids	32.2	283	-	-	-
Pulmonary embolism	0.6	5	1.5	13	0.38
Arthritis	-	-	27.2	231	-
White leg of pregnancy**	-	-	0.6	3	-

% (n) based on number of participants with a history of the medical condition at baseline and at follow up.
[a] P value based on difference in prevalence of medical conditions between baseline and follow up
*Swollen leg post pregnancy based on 381 female participants at baseline and 476 female participants at follow up
**White leg of pregnancy determined in 476 female participants at follow up. Prevalence of condition was not measured at the baseline phase of the study.

TABLE 10.6 13 YEAR INCIDENCE OF C2 VARICOSE VEINS AT FOLLOW UP BY HISTORY OF MEDICAL CONDITIONS AT BASELINE

MEDICAL CONDITION AT BASELINE	13 YEAR INCIDENCE C2 VARICOSE VEINS % (95% CI)	n (N)	P VALUE *	UNADJUSTED OR [a] (95% CI)	ADJUSTED OR [b] (95% CI)
DEEP VEIN THROMBOSIS					
No	17.6 (14.4-21.5)	96 (544)	0.02	1.00	1.00
Yes	50.0 (18.3-110.8)	5 (10)		4.67 (1.32-16.44)	3.46 (0.96-12.45)
PHLEBITIS					
No	17.4 (14.2-21.2)	94 (539)	0.03	1.00	1.00
Yes	42.9 (17.4-89.1)	6 (14)		3.55 (1.20-10.47)	2.78 (0.92-8.42)
PULMONARY EMBOLISM					
No	18.1 (14.8-22.0)	100 (551)	0.33	1.00	1.00
Yes	50.0 (2.5-246.6)	1 (2)		4.51 (0.28-72.72)	3.89 (0.24-63.14)
HAEMORRHOIDS					
No	18.3 (14.3-23.0)	69 (377)	0.95	1.00	1.00
Yes	18.1 (12.6-25.2)	32 (177)		0.99 (0.62-1.57)	0.81 (0.50-1.31)
INGUINAL HERNIA					
No	17.9 (14.6-21.9)	94 (524)	0.62	1.00	1.00
Yes	23.3 (10.2-46.2)	7 (30)		1.39 (0.58-3.34)	1.21 (0.49-2.96)
SWOLLEN LEG					
No	16.9 (13.6-20.8)	86 (509)	0.22	1.00	1.00
Yes	27.6 (12.8-52.4)	8 (29)		1.87 (0.80-4.37)	1.83 (0.78-4.34)
FRACTURED LEG					
No	18.4 (14.9-22.4)	92 (501)	0.95	1.00	1.00
Yes	18.0 (8.8-33.0)	9 (50)		0.98 (0.46-2.08)	0.99 (0.46-2.14)

n= number of participants with medical condition at baseline and C2 varicose veins at follow up, (N) = number of participants medical condition at baseline

* P value based on chi square test for association between medical condition at baseline and incidence of C2 varicose veins at follow up. $p<0.05$ denotes statistical significance

[a] Unadjusted odds ratio = crude odds ratio for the risk of developing C2 varicose veins with no adjustment for age or sex

[b] Adjusted odds ratio = odds ratio for the risk of developing C2 varicose veins adjusted for age and sex

TABLE 10.7 13 YEAR INCIDENCE OF C3-C6 CHRONIC VENOUS INSUFFICIENCY AT FOLLOW UP BY MEDICAL CONDITIONS AT BASELINE

MEDICAL CONDITION AT BASELINE	13 YEAR INCIDENCE C3-C6 CVI % (95% CI)	n (N)	P VALUE *	UNADJUSTED OR [a] (95% CI)	ADJUSTED OR [b] (95% CI)
DEEP VEIN THROMBOSIS					
No	9.1 (6.8-12.0)	49 (536)	0.58	1.00	1.00
Yes	11.1 (0.6-54.8)	1 (9)		1.24 (0.15-10.14)	0.80 (0.09-6.82)
PHLEBITIS					
No	8.7 (6.4-11.4)	46 (531)	0.10	1.00	1.00
Yes	23.1 (5.9-62.8)	3 (13)		3.16 (0.84-11.90)	2.37 (0.60-9.43)
PULMONARY EMBOLISM					
No	9.2 (6.9-12.1)	50 (542)	0.82	1.00	1.00
Yes	0	0 (2)		0	0
HAEMORRHOIDS					
No	8.6 (6.0-12.1)	32 (370)	0.54	1.00	1.00
Yes	10.3 (6.3-15.9)	18 (175)		1.21 (0.66-2.22)	0.95 (0.50-1.79)
INGUINAL HERNIA					
No	8.2 (5.9-10.9)	42 (515)	0.01	1.00	1.00
Yes	26.7 (12.4-50.6)	8 (30)		4.09 (1.72-9.76)	3.14 (5.9-10.9)
SWOLLEN LEG					
No	8.9 (6.6-11.8)	45 (504)	0.62	1.00	1.00
Yes	4.0 (0.2-19.7)	1 (25)		0.43 (0.06-3.22)	0.38 (0.05-2.92)
FRACTURED LEG					
No	8.7 (7.4-13.0)	43 (493)	0.58	1.00	1.00
Yes	12.2 (5.0-25.5)	6 (49)		1.46 (0.59-3.63)	1.49 (0.59-3.80)

n= number of participants with medical condition at baseline and C3-C6 CVI at follow up, (N) = number of participants medical condition at baseline

* P value based on chi square test for association between medical condition at baseline and incidence of C3-C6 CVI at follow up. $p<0.05$ denotes statistical significance

[a] Unadjusted odds ratio = crude odds ratio for the risk of developing C3-C6 CVI with no adjustment for age or sex

[b] Adjusted odds ratio = odds ratio for the risk of developing C3-C6 CVI, adjusted for age and sex

FIGURE 10.2 PREGNANCY AT BASELINE AND FOLLOW UP

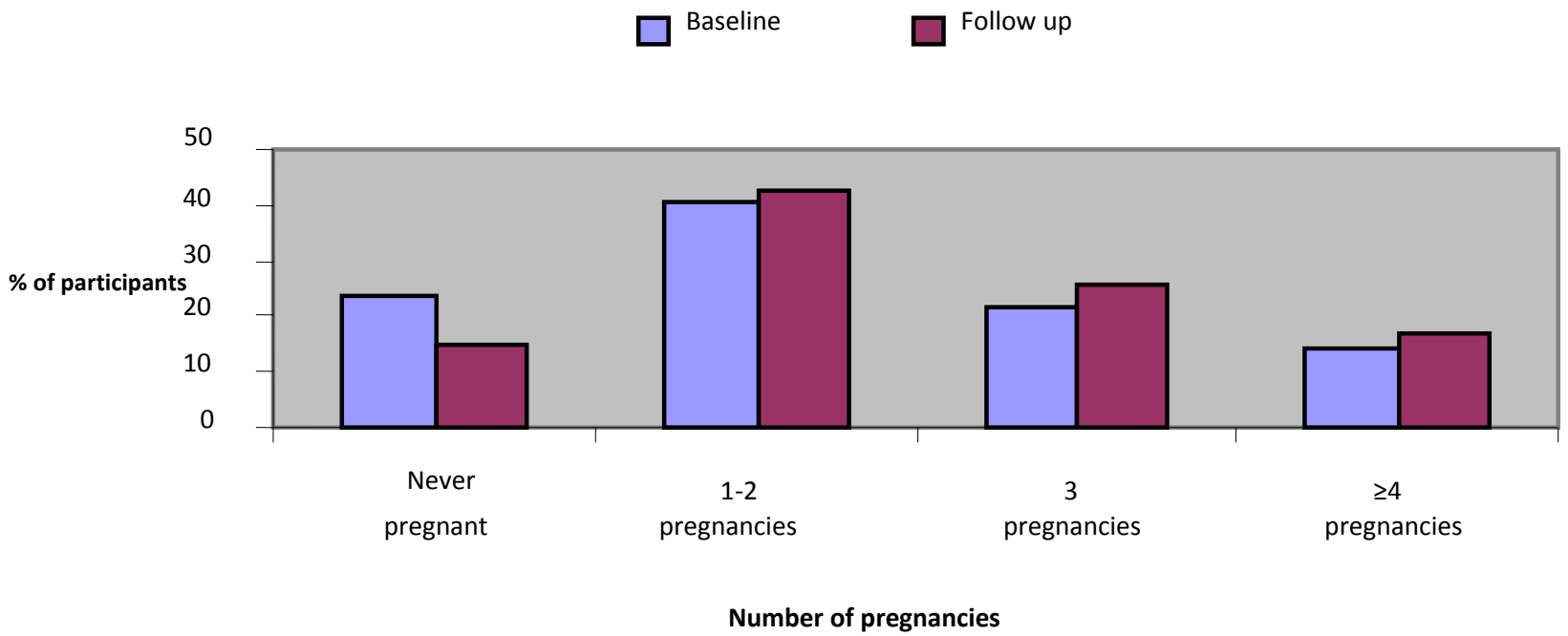


TABLE 10.8 13 YEAR INCIDENCE OF C2 VARICOSE VEINS AT FOLLOW UP ACCORDING TO PREGNANCY AT BASELINE

	13 YEAR INCIDENCE C2 VARICOSE VEINS		P TREND [*]	UNADJUSTED OR [a]	ADJUSTED OR [b]
PREGNANCY	**% (95% CI)**	**n (N)**		**(95% CI)**	**(95% CI)**
NUMBER OF PREGNANCIES AT BASELINE					
0	16.7 (9.7-26.9)	15 (90)	0.14	1.00	1.00
1-2	16.3 (10.5-24.3)	22 (135)		0.97 (0.48-2.00)	0.63 (0.29-1.37)
3	20.0 (11.1-33.3)	13 (65)		1.25 (0.55-2.85)	0.72 (0.29-1.75)
≥ 4	27.3 (14.8-46.4)	12 (44)		1.88 (0.79-4.45)	1.05 (0.41-2.67)
PREGNANCIES DURING FOLLOW UP					
0	20.7 (15.6-27.0)	52 (251)	0.26	1.00	1.00
1	13.3 (4.2-32.2)	4 (30)		0.23 (0.03-1.84)	0.43 (0.05-3.71)
2	7.1 (0.4-35.2)	1 (14)		0.12 (0.01-1.73)	0.32 (0.20-5.48)
3	22.2 (3.7-73.4)	2 (9)		0.43 (0.04-4.64)	1.35 (0.11-17.30)

n= number of participants by number of pregnancies at baseline and C2 varicose veins at follow up, (N) = number of participants by number of pregnancies at baseline

[*] P value based on chi square test for linear association between number of pregnancies at baseline and incidence of C2 varicose veins at follow up. $p<0.05$ denotes statistical significance

[a] Unadjusted odds ratio = crude odds ratio for the risk of developing C2 varicose veins with no adjustment for age or sex

[b] Adjusted odds ratio = odds ratio for the risk of developing C2 varicose veins, adjusted for age and sex

Incidence of C2 varicose veins based on the number of new cases of C2 varicose veins at follow up divided by the number of participants free from C2 varicose veins at baseline.

TABLE 10.9 13 YEAR INCIDENCE OF C3-C6 CHRONIC VENOUS INSUFFICIENCYAT FOLLOW UP ACCORDING TO PREGNANCY AT BASELINE

	13 YEAR INCIDENCE C3-C6 CVI		P TREND *	UNADJUSTED OR [a]	ADJUSTED OR [b]
PREGNANCY	**% (95% CI)**	**n (N)**		**(95% CI)**	**(95% CI)**
NUMBER OF PREGNANCIES AT BASELINE					
0	5.6 (2.1-12.4)	5 (89)	0.42	1.00	1.00
1-2	9.0 (4.8-15.2)	12 (134)		1.65 (0.56-4.86)	0.89 (0.28-2.79)
3	9.2 (3.7-19.2)	6 (65)		1.71 (0.50-5.86)	0.78 (0.21-2.85)
≥ 4	9.3 (3.0-22.4)	4 (43)		1.72 (0.44-6.77)	0.71 (0.67-3.04)
PREGNANCIES DURING FOLLOW UP					
0	8.5 (5.4-12.7)	21 (248)	0.88	1.00	1.00
1	3.3 (0.2-16.4)	1 (30)		0.14 (0.01-2.67)	0.39 (0.02-8.54)
2	0	0 (14)		0	0
3	11.1 (0.6-54.8)	1 (9)		0.50 (0.02-10.25)	0.43 (0.01-18.76)

n= number of participants by number of pregnancies at baseline and C3-C6 CVI follow up, (N) = number of participants by number of pregnancies at baseline

* P value based on chi square test for linear association between number of pregnancies at baseline and incidence of C3-C6 CVI at follow up. $p<0.05$ denotes statistical significance

[a] Unadjusted odds ratio = crude odds ratio for the risk of developing C2 varicose C3-C6 CVI adjusted for age and sex.

Incidence of C3-C6 CVI based on the number of new cases of C3-C6 CVI at follow up, divided by the number of participants free from C2 varices and C3-C6 CVI at baseline.

TABLE 10.10 13 YEAR INCIDENCE OF C2 VARICOSE VEINS AT FOLLOW UP ACCORDING TO MOBILITY AT WORK AT BASELINE

	13 YEAR INCIDENCE C2 VARICOSE VEINS		P VALUE *	UNADJUSTED OR [a]	ADJUSTED OR [b]
MOBILITY AT WORK AT BASELINE	**% (95% CI)**	**n (N)**		**(95% CI)**	**(95% CI)**
SITTING					
< 50% of the day	18.8 (14.3-24.1)	57 (304)	0.71	1.00	1.00
> 50% of the day	17.5 (12.9-23.3)	44 (251)		0.92 (0.60-1.42)	0.95 (0.61-1.48)
STANDING					
< 50% of the day	18.3 (14.4-22.8)	74 (405)	0.94	1.00	1.00
> 50% of the day	18.0 (12.1-25.8)	27 (150)		0.98 (0.60-1.60)	0.99 (0.61-1.63)
WALKING					
< 50% of the day	18.3 (14.5-22.8)	75 (410)	0.95	1.00	1.00
> 50% of the day	18.1 (12.0-26.1)	26 (144)		0.98 (0.60-1.61)	0.95 (0.58-1.56)
HEAVY LIFTING					
< 50% of the day	17.1 (14.2-21.7)	86 (486)	0.42	1.00	1.00
> 50% of the day	14.9 (12.6-35.0)	15 (69)		1.29 (0.70-2.40)	1.31 (0.70-2.45)

n= number of participants in mobility at work group at baseline and C2 varicose veins at follow up, (N) = number of participants in mobility at work group at baseline

[*] P value based on chi square test for association between mobility at work at baseline and incidence of C2 varicose veins at follow up. $p<0.05$ denotes statistical significance

[a] Unadjusted odds ratio = crude odds ratio for the risk of developing C2 varicose veins with no adjustment for age or sex

[b] Adjusted odds ratio = odds ratio for the risk of developing C2 varicose veins adjusted for age and sex

Incidence of C2 varicose veins based on the number of new cases of C2 varicose veins at follow up divided by the number of participants free from C2 varicose veins at baseline.

TABLE 10.11 13 YEAR INCIDENCE OF C3-C6 CHRONIC VENOUS INSUFFICIENCY AT FOLLOW UP ACCORDING TO MOBILITY AT WORK AT BASELINE

	13 YEAR INCIDENCE C3-C6 CVI		P VALUE *	UNADJUSTED OR [a]	ADJUSTED OR [b]
MOBILITY AT WORK AT BASELINE	% (95% CI)	n/N		(95% CI)	(95% CI)
SITTING					
< 50% of the day	10.4 (7.2-14.6)	31/297	0.32	1.00	1.00
> 50% of the day	7.6 (4.7-11.7)	19/249		0.71 (0.39-1.29)	0.75 (0.41-1.38)
STANDING					
< 50% of the day	9.2 (6.6-12.6)	37/401	0.92	1.00	1.00
> 50% of the day	9.0 (5.0-14.9)	13/145		0.97 (0.50-1.88)	0.94 (0.48-1.87)
WALKING					
< 50% of the day	8.7 (6.1-11.9)	35/403	0.51	1.00	1.00
> 50% of the day	10.6 (6.1-17.0)	15/142		1.24 (0.66-2.35)	1.18 (0.62-2.27)
HEAVY LIFTING					
< 50% of the day	9.0 (6.6-12.0)	43/479	0.70	1.00	1.00
> 50% of the day	10.4 (4.6-20.7)	7/67		1.18 (0.51-2.75)	1.15 (0.48-2.74)

n= number of participants in mobility at work group at baseline and C3-C6 CVI at follow up, (N) = number of participants in mobility at work group at baseline

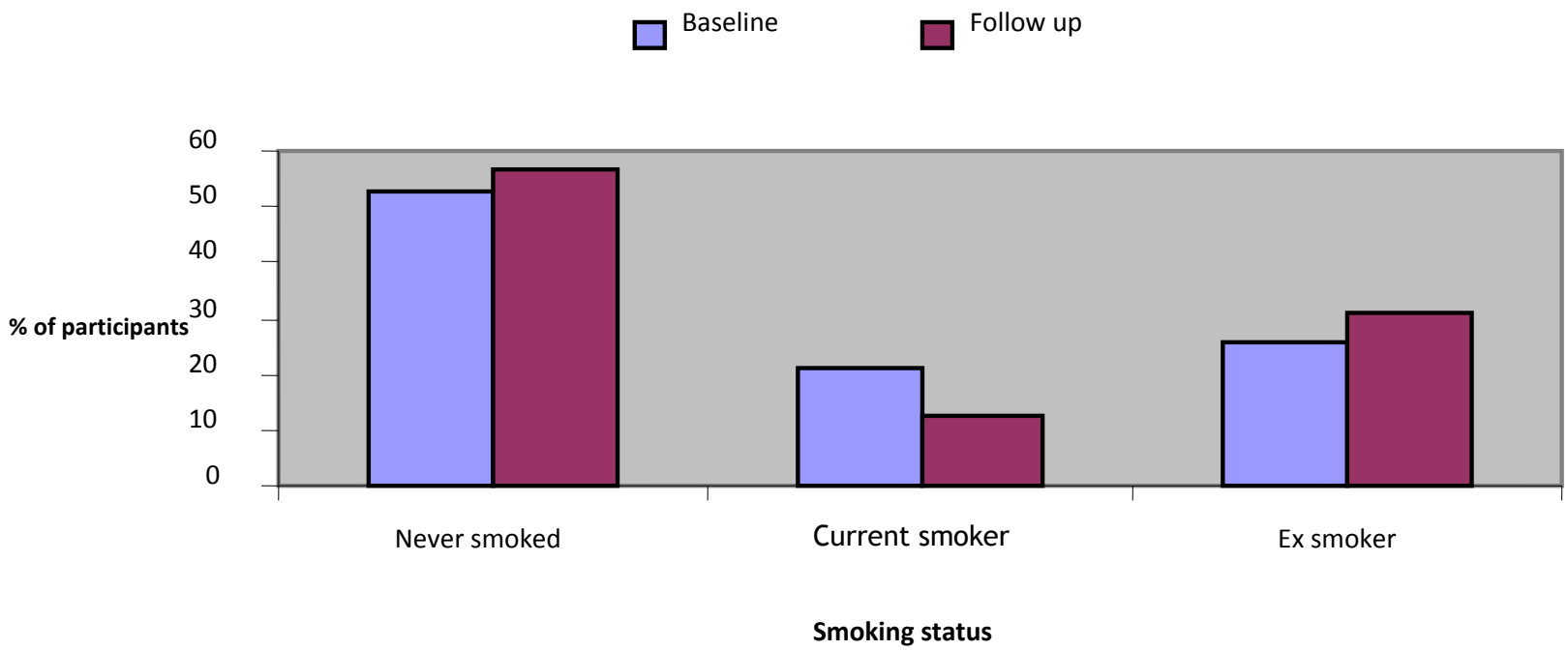
* P value based on chi square test for association between mobility at work at baseline and incidence of C3-C6 CVI at follow up. $p<0.05$ denotes statistical significance

[a] Unadjusted odds ratio = crude odds ratio for the risk of developing C3-C6 CVI with no adjustment for age or sex

[b] Adjusted odds ratio = odds ratio for the risk of developing C3-C6 CVI adjusted for age and sex

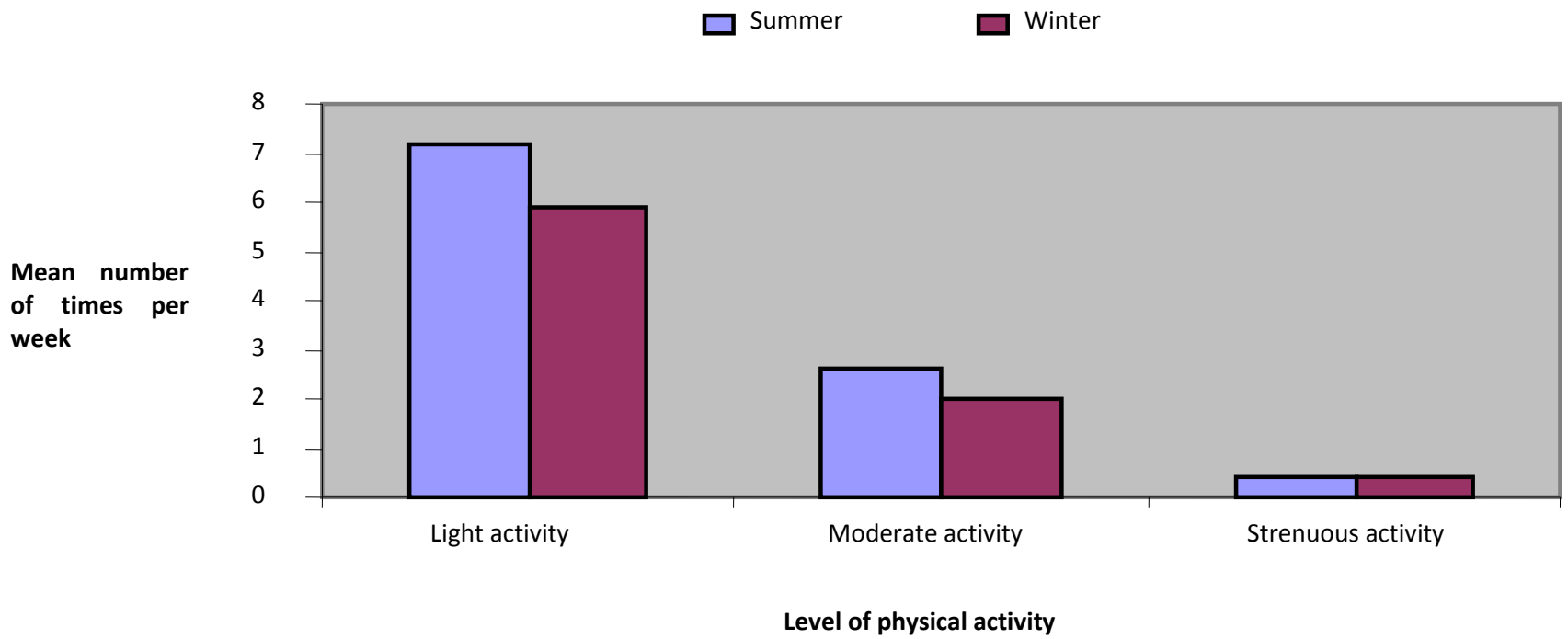
Incidence of C3-C6 CVI based on the number of new cases of C3-C6 CVI at follow up, divided by the number of participants free from C2 varices and C3-C6 CVI at baseline.

FIGURE 10.3 CHANGES IN SMOKING STATUS FROM BASELINE TO FOLLOW UP



History of medical conditions at baseline and follow up stages of the study in 880 participants

FIGURE 10.4 PHYSICAL ACTIVITY LEVELS IN PARTICIPANTS AT FOLLOW UP



Light physical activity = walking, gardening, light DIY, yoga
Moderate physical activity = badminton, cycling, golf, jogging, swimming, tennis
Strenuous physical activity = competitive running, fields sports, sports training, squash

CHAPTER 11: RISK FACTORS AND INCIDENCE OF VENOUS REFLUX

11.1 CHAPTER OUTLINE

This chapter examines the association between risk factors for venous disease at baseline and the development of venous reflux ≥ 0.5s duration at follow up. Risk factors measured in the Edinburgh Vein Study include body mass index (BMI), pregnancy, oestrogen use including oral contraceptives (OC) and hormone replacement therapy (HRT), smoking, family history of venous disease, mobility at work, history of medical conditions associated with venous disease, physical activity and bowel movement. For each risk factor measured at baseline, the incidence of deep only, superficial only and combined deep and superficial reflux at follow up, is presented. Where possible, changes in risk factors during the follow up period are examined to check for any association with the development of venous reflux at follow up. Bowel movement was measured at baseline only while physical activity was measured at follow up only. Changes to these two risk factors during the follow up period could not be measured.

11.2 BODY MASS INDEX (BMI)

Body mass index (BMI) at baseline was not significantly associated with venous reflux ≥0.5s duration at follow up. The incidence of all reflux was 0% in those who were underweight (n=3), 9.6% (95% CI 5.5-15.7) in those who were normal weight (n=153), 17.5% (95% CI 11.0-26.6) in those who were overweight (n=116) and 11.6% (95% CI 4.3-25.8) in participants who were obese (n=44) at baseline (p trend=0.25). Furthermore, when analysed as a continuous variable, BMI at baseline did not differ significantly between those who developed reflux at follow up (mean (SD) 26.2 (4.1) kg/m^2) and those who did not (mean (SD) 25.6 (4.2) kg/m^2) (p=0.43). Table 11.1 provides a detailed summary of the incidence of reflux by vein segments by BMI group at baseline. No participant who was underweight at baseline developed deep, superficial or combined reflux at follow up. When reflux was categorised according to venous system affected, the number of participants was small, and incidence of deep (p=0.29), superficial (p=0.49) and combined reflux (p=0.20) was not associated with BMI group at baseline.

Figure 11.1 shows that change in BMI group during follow up was not significantly associated with incidence of any reflux (p=0.29), deep reflux only (p=0.49), superficial reflux only (p=0.13) nor combined reflux (p=0.54). When analysed as a continuous variable, there were no significant differences between the mean change in BMI during follow up in those with any reflux (p=0.44), deep reflux only (p=0.37), superficial reflux only (p=0.22) or combined deep and superficial reflux (p=0.20) at follow up (data not shown).

11.3 FAMILY HISTORY OF VENOUS DISEASE

Of 184 participants with no family history, 21 developed reflux ≥0.5 s duration at follow up, giving a 13 year incidence of 11.4% (95% CI 7.2-17.1). Of the 114 participants with a maternal or paternal family history, 17 developed reflux at follow up giving an incidence of 14.9% (95% CI 9.0-23.4). The chi square test showed there was no significant association between family history and incidence of reflux (p=0.48). Incidence of reflux by specific vein segments, according to family history at baseline is presented in Table 11.2. When analysed by venous system affected, family history of venous disease was not associated with increased incidence of reflux (all p≥0.50).

11.4 MEDICAL HISTORY

Table 11.3 presents the 13 year incidence of deep, superficial and combined venous reflux ≥0.5s duration according to history of medical conditions at baseline. None of the conditions were associated with incidence of deep or superficial venous reflux. However, history of DVT was associated with increased incidence of combined venous reflux. Among participants with no DVT at baseline, the incidence of combined reflux was 1.0% (95% CI 0.2-2.7) at follow up compared to 33.3% (95% CI 1.7-164.4) in those with a history of DVT (p=0.04). However, it should be noted that the number of participants with a history of DVT was very small (n=3), probably accounting for the high incidence and large confidence intervals observed.

11.5 PREGNANCY

The 13-year incidence of venous reflux ≥0.5s duration was 17.4% (95% CI 8.1-33.0) in women who had never been pregnant (n=46), 13.4% (95% CI 6.6-24.7) in women who had 1-2 pregnancies (n=67), 13.2% (95% CI 4.8-29.2) in those with 3 pregnancies (n=38) and 12.5% (95% CI 3.2-34.0) in women who had been pregnant at least 4 times at baseline (n=24) (p trend=0.55). The incidence of venous reflux in specific vein segments by pregnancy at baseline is presented in Table 11.4. Very few women developed deep reflux (n=4) or combined reflux (n=2) and neither were associated with pregnancy (p=0.32 and p=0.74 respectively). The incidence of superficial reflux was higher in those with a previous pregnancy but this association was not statistically significant (p=0.85).

Pregnancy during the 13 year follow up was not associated with development of venous reflux. The incidence was 14.0% (95% CI 8.7-21.4) in women with no further pregnancies (n=136), 0% in those with 1 or 2 further pregnancies (n=16), 80.0% (95% CI 25.4-193.0) in those with 3 further pregnancies (n=5) and 50.0% (95% CI 2.5-246.6) in those with 4 further pregnancies (n=2) between baseline and follow up (p trend=0.56). It should be noted that only 23 women experienced one or more pregnancies during follow up, thus accounting for the high incidence and wide confidence intervals. When analysed by type of reflux, pregnancy during the follow up period had no significant effect on the incidence of deep venous reflux (p=0.75), superficial reflux (p=0.67) nor combined reflux (p=0.84).

11.6 ORAL CONTRACEPTIVE USE

Oral contraceptive use at baseline was not associated with the development of venous reflux ≥0.5s duration, with an overall incidence of 19.5% (95% CI 9.1-37.0) in female participants who had never used oral contraceptives (n=123) compared to 11.5% (95% CI 6.3-19.6) in previous oral contraceptive users (n=44) (p=0.32). Oral contraceptive use remained insignificant for the development of deep (p=0.35), superficial (p=0.06) and combined reflux (p=0.72). Additionally change in oral contraceptive use during follow up was not associated with venous reflux (p=0.55) (data not shown).

11.7 HORMONE REPLACEMENT THERAPY (HRT)

Previous HRT users (n=41) appeared to be more likely to develop venous reflux ≥0.5s duration at follow up with an incidence of 30.8% (95% CI 9.8-74.2) compared to 12.7% (95% CI 7.7-19.6) in non HRT users (n=127). However, this finding did not reach statistical significance. The incidence of deep (p=0.31), superficial (p=0.40) and combined reflux (p=0.16) did not differ significantly according to HRT use at baseline or during follow up (data not shown).

11.8 MOBILITY AT WORK

Baseline mobility at work had no significant effect on incidence of venous reflux ≥0.5s duration at follow up (p=0.55). Results in Table 11.5 show that the 13-year incidence of deep, superficial and combined reflux was similar in all participants regardless of mobility at work at baseline (all p≥0.50).

11.9 SMOKING

There was no significant association between smoking at baseline and reflux, with an incidence of 13.6% (95% CI 8.7-20.2) in those who had never smoked (n=162), 13.6% (95% CI 7.1-23.6) in ex-smokers (n=81) and 9.5% (95% CI 3.9-19.8) in current smokers (n=63) (p trend=0.89). Table 11.6 displays incidence of reflux by vein segment and shows that smoking was not significantly associated with the development of deep (p=0.42), superficial (p=0.79) or combined reflux (p=0.65). Incidence of reflux did not differ significantly in participants who had either started (n=23) or stopped smoking (n=4) during follow up (p≥0.05, data not shown).

11.10 BOWEL HABIT

Bowel habit at baseline was not significantly associated with incidence of venous reflux ≥0.5s duration at follow up. The incidence of venous reflux was 12.8% (95% CI 9.0-17.7) in those who had to strain to start a bowel movement only occasionally compared to 12.2% (95% CI 4.5-27.0) in those who had to strain more than half of the time (p=0.91). For straining to finish a bowel movement, the incidence of reflux at follow up as 12.4% (95% CI 8.7-17.1) in those who strained to finish only occasionally compared to 16.1% (95% CI 5.9-35.7) in those who had to strain to finish more than half of the time (p=0.36). Neither isolated deep (p=0.38), superficial (p=0.60) nor combined reflux (p=0.39) were associated with strained bowel movement.

11.11 PHYSICAL ACTIVITY

Activity levels did not differ significantly in participants with and without venous reflux at follow up. Light exercise was performed a mean (SD) 6.8 (6.5) times per week in those with no reflux compared to 6.4 (9.6) in participants with reflux (P=0.83). At follow up, moderate physical activity was performed 2.9 (6.7) and 2.4 (3.6) times per week in those with and without reflux (p=0.66). Strenuous physical activity was performed to the same extent in all participants, with a mean of 0.5 (1.2) times per week in all participants regardless of venous reflux at follow up (p=0.84). Physical activity levels did not differ significantly in participants with and without isolated deep, superficial or combined reflux at follow up (p≥0.05, data not shown).

11.12 CHAPTER SUMMARY

This chapter has discussed the incidence of deep, superficial and combined venous reflux ≥ 0.5s duration in association with risk factors measured at baseline. Changes in risk factors during the 13-year follow up period of the study were also analysed to determine their effect on the incidence of venous reflux. The only risk factor which appeared to be associated with venous reflux was history of DVT at baseline, although the numbers with DVT were too small to draw any meaningful conclusions. Body mass index, family history of venous disease, mobility at work, pregnancy, female hormone use, smoking and bowel movement at baseline appeared to have no impact on the incidence of venous reflux at follow up.

TABLE 11.1 13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS DURATION AT FOLLOW UP BY BODY MASS INDEX (BMI) GROUP AT BASELINE

	13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS						
	NORMAL WEIGHT (N = 150) [a]		OVERWEIGHT (N = 114) [a]		OBESE (N = 43) [a]		P VALUE*
PATTERN OF REFLUX	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	
DEEP REFLUX ONLY [b]	1.3 (0.2-4.4)	2	5.3 (2.1-10.9)	6	0	0	0.64
CFV origin	0.7 (0.03-3.3)	1	0	0	0	0	
FV lower thigh	0	0	0.9 (0.04-4.3)	1	0	0	
POP lower	0.7 (0.03-3.3)	1	1.7 (0.3-5.8)	2	0	0	
POP upper + lower	0	0	2.6 (0.7-7.2)	3	0	0	
SUPERFICIAL REFLUX ONLY [c]	8.8 (4.5-15.6)	10	10.5 (5.7-17.9)	12	11.6 (4.3-25.8)	5	0.20
GSV origin	0	0	0.9 (0.04-4.3)	1	2.3 (0.1-11.5)	1	
GSV lower thigh	1.4 (0.2-4.5)	2	5.3 (2.1-10.9)	6	4.6 (0.8-15.4)	2	
SSV	1.4 (0.2-4.5)	2	0.9 (0.04-4.3)	1	0	0	
GSV origin + GSV lower thigh	1.4 (0.2-4.5)	2	2.6 (0.7-7.2)	3	2.3 (0.1-11.5)	1	
GSV lower thigh + SSV	1.4 (0.2-4.5)	2	0.9 (0.04-4.3)	1	0	0	
GSV origin + GSV lower thigh + SSV	1.4 (0.2-4.5)	2	0	0	2.3 (0.1-11.5)	1	

[a] Normal weight = BMI 18.50-24.99 kg/m^2, Overweight = BMI 25.00-29.99 kg/m^2, obese = BMI ≥ 30 kg/m^2

% (95% CI) = 13-year incidence of reflux ≥ 0.5 seconds duration by vein segment affected according to BMI group at baseline

n = number of participants with no reflux at baseline but reflux in vein segment at follow up according to BMI group at baseline

* P value based on chi square test for linear trend for difference in incidence of venous reflux by BMI group at baseline

[b] Deep reflux only = reflux ≥ 0.5s in CFV, FV or POP + no reflux in GSV or SSV at follow up, based on 309 participants: 150 normal weight, 114 overweight, 42 obese

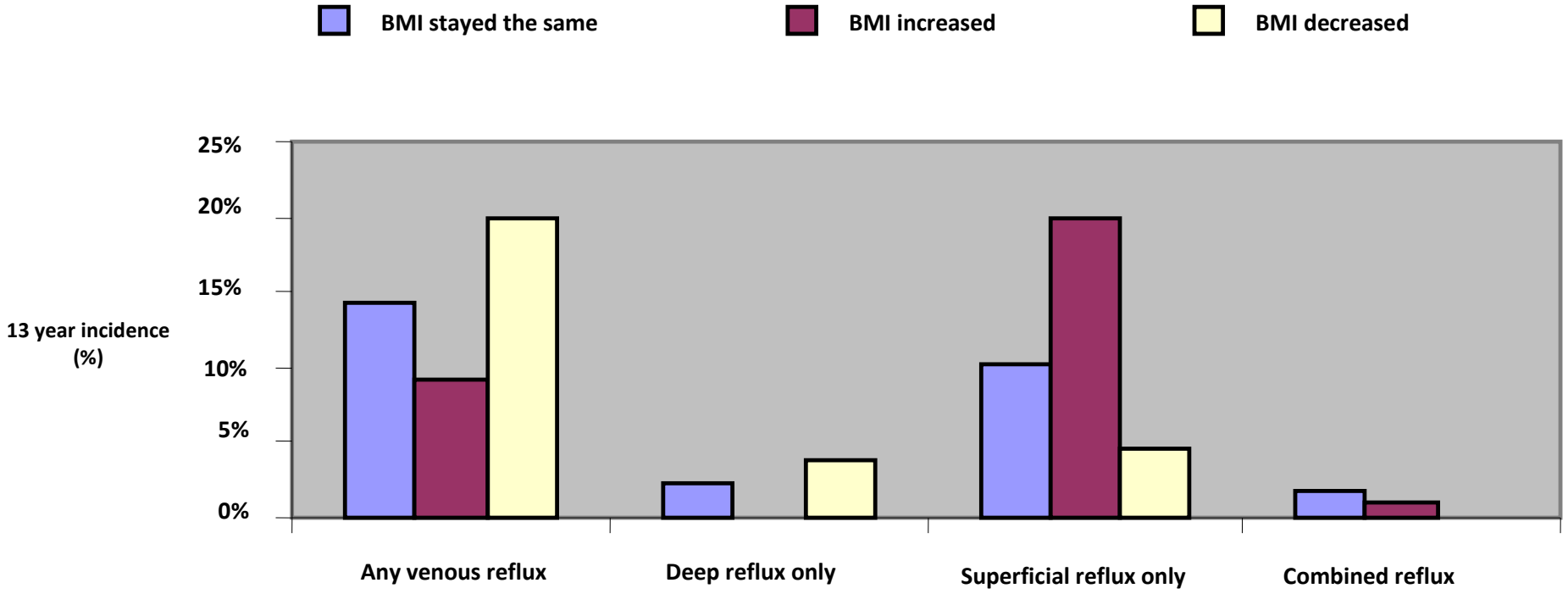
[c] Superficial reflux only = reflux ≥ 0.5s in GSV or SSV + no reflux in CFV, FV or POP at follow up, based on 306 participants: 146 normal weight, 114 overweight, 43 obese

TABLE 11.1 13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS DURATION AT FOLLOW UP BY BODY MASS INDEX (BMI) GROUP AT BASELINE (CONTINUED)

	13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS						
	NORMAL WEIGHT (N = 150) [a]		OVERWEIGHT (N = 114) [a]		OBESE (N = 43) [a]		P VALUE*
PATTERN OF REFLUX	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	
COMBINED REFLUX [b]	1.4 (0.2-4.5)	2	1.8 (0.3-5.8)	2	0	0	0.70
POP upper + GSV lower thigh	0.7 (0.03-3.4)	1	0	0	0	0	
POP lower + SSV	0.7 (0.03-3.4)	1	0	0	0	0	
POP upper + GSV lower thigh + SSV	0	0	0.9 (0.04-4.3)	1	0	0	

[a] Normal weight = BMI 18.50-24.99 kg/m^2, Overweight = BMI 25.00-29.99 kg/m^2, obese = BMI ≥ 30 kg/m^2
% (95% CI) = 13-year incidence of reflux ≥ 0.5 seconds duration by vein segment affected according to BMI group at baseline
n = number of participants with no reflux at baseline but reflux in vein segment at follow up according to BMI group at baseline
* P value based on chi square test for linear trend for difference in incidence of venous reflux by BMI group at baseline
[b] Combined reflux = reflux ≥0.5s in CFV, FV or POP + reflux ≥ 0.5s in GSV or SSV at follow up, based on 304 participants: 146 normal weight, 113 overweight, 42 obese

FIGURE 11.1 INCIDENCE OF VENOUS REFLUX AT FOLLOW UP ACCORDING TO CHANGE IN BODY MASS INDEX GROUP



Any venous reflux = reflux ≥ 0.5s in any one of CFV, FV, POP, GSV or SSV in any leg at follow up
Deep reflux only = reflux ≥ 0.5s in CFV, FV or POP + no reflux in GSV or SSV at follow up
Superficial reflux only = reflux ≥ 0.5s in GSV or SSV + no reflux in CFV, FV or POP at follow up
Combined reflux = reflux ≥ 0.5s in CFV, FV or POP + reflux ≥ 0.5 s in GSV or SSV at follow up

TABLE 11.2 13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS AT FOLLOW UP, ACCORDING TO FAMILY HISTORY OF VENOUS DISEASE AT BASELINE

	13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS				
	NO FAMILY HISTORY (N=184)		FAMILY HISTORY (N=114)		P VALUE*
PATTERN OF REFLUX	% (95% CI)	n	% (95% CI)	n	
DEEP REFLUX ONLY [a]	2.2 (0.7-5.2)	4	3.4 (1.1-8.2)	4	0.40
CFV origin	0.5 (0.1-2.7)	1	0	0	
FV lower thigh	0	0	0.9 (0.04-4.3)	1	
POP lower	1.1 (0.2-3.6)	2	0.9 (0.04-4.3)	1	
POP upper + lower	0.5 (0.1-2.7)	1	1.7 (0.3-5.8)	2	
SUPERFICIAL REFLUX ONLY [b]	2.7 (1.0-6.0)	15	6.0 (3.1-10.4)	11	0.34
GSV origin	1.1 (0.2-3.6)	2	0	0	
GSV lower thigh	2.7 (1.0-6.0)	5	3.5 (1.1-8.5)	4	
SSV	0.5 (0.1-2.7)	1	1.7 (0.3-5.8)	2	
GSV origin + GSV lower thigh	1.1 (0.2-3.6)	2	3.5 (1.1-8.5)	4	
GSV origin + SSV	0	0	0	0	
GSV lower thigh + SSV	1.6 (0.4-4.4)	3	0	0	
GSV origin + lower thigh + SSV	1.1 (0.2-3.6)	2	0.9 (0.04-4.3)	1	

% (95% CI) = 13-year incidence of reflux by vein segment affected according to family history of venous disease at baseline in either first-degree relative

n = number of participants with no reflux at baseline but reflux in each vein segment at follow according to family history of venous disease at baseline

*P value based on test for chi squared test for difference in incidence of venous reflux in any leg at follow up according to family history of venous disease at baseline

[a] Deep reflux only = reflux ≥ 0.5s in CFV, FV or POP + no reflux in GSV or SSV at follow up, based on 301 participants: no family history (184), family history of venous disease (114)

[b] Superficial reflux = reflux ≥ 0.5s in GSV or SSV + no reflux in CFV, FV or POP at follow up, based on 298 participants: no family history (184), family history of venous disease (114)

TABLE 11.2 13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS AT FOLLOW UP, ACCORDING TO FAMILY HISTORY OF VENOUS DISEASE AT BASELINE (CONTINUED)

	13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS				
	NO FAMILY HISTORY (N=184)		FAMILY HISTORY (N=114)		P VALUE*
PATTERN OF REFLUX	% (95% CI)	n	% (95% CI)	n	
COMBINED REFLUX [a]	1.1 (0.2-3.6)	2	1.8 (0.3-5.8)	2	0.50
POP lower + GSV lower thigh	0	0	0.9 (0.04-4.3)	1	
POP lower + SSV	0	0	0.9 (0.04-4.3)	1	
POP upper + GSV lower thigh + SSV	0.5 (0.1-2.7)	1	0	0	
CFV + POP upper + lower + GSV origin + GSV lower thigh	0.5 (0.1-2.7)	1	0	0	

% (95% CI) = 13-year incidence of reflux by vein segment affected according to family history of venous disease at baseline in either first-degree relative
n = number of participants with no reflux at baseline but reflux in each vein segment at follow according to family history of venous disease at baseline
*P value based on test for chi squared test for difference in incidence of venous reflux in any leg at follow up according to family history of venous disease at baseline
[a] Combined reflux = reflux ≥ 0.5s in CFV, FV or POP + reflux ≥ 0.5s in GSV or SSV at follow up, based on 296 participants: no family history , family history of venous disease (114)

TABLE 11.3 13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS DURATION AT FOLLOW UP BY HISTORY OF MEDICAL CONDITIONS AT BASELINE

	13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS								
	DEEP REFLUX ONLY [a]			SUPERFICIAL REFLUX ONLY [b]			COMBINED REFLUX [c]		
MEDICAL CONDITION	% (95% CI)	n (N)	P value*	% (95% CI)	n (N)	P value*	% (95% CI)	n (N)	P value*
DEEP VEIN THROMBOSIS									
- No	2.6 (1.2-5.0)	8 (304)	0.92	8.6 (5.8-12.5)	26 (309)	0.24	1.0 (0.2-2.7)	3 (299)	0.04
- Yes	0 (0-99.9)	0 (3)		33.3 (1.7-164.4)	1 (3)		33.3 (1.7-164.4)	1 (3)	
PHLEBITIS									
- No	2.6 (1.2-5.0)	8 (302)	0.85	8.4 (5.5-12.2)	25 (299)	0.09	1.3 (0.4-3.2)	4 (297)	0.92
- Yes	0 (0-49.9)	0 (6)		33.3 (5.6-110.1)	2 (6)		0 (0-49.9)	0 (6)	
PULMONARY EMBOLISM									
- No	2.6 (1.2-4.9)	8 (308)	0.97	8.9 (6.0-12.7)	27 (305)	0.91	1.3 (0.4-3.2)	4 (303)	0.99
- Yes	0 (0-299.6)	0 (1)		0 (0-299.6)	0 (1)		0 (0-299.6)	0 (1)	
HAEMORRHOIDS									
- No	3.3 (1.4-6.4)	7 (215)	0.24	9.3 (5.8-14.1)	20 (215)	0.82	0.9 (0.2-3.1)	2 (300)	0.59
- Yes	1.1 (0.1-5.2)	1 (91)		7.7 (3.4-15.2)	7 (91)		2.2 (0.4-7.3)	2 (91)	
HERNIA									
- No	2.4 (1.1-4.8)	7 (286)	0.45	9.2 (6.0-12.7)	26 (284)	0.43	1.4 (0.4-3.4)	4 (282)	0.75
- Yes	4.5 (0.2-22.4)	1 (22)		4.8 (0.2-23.5)	1 (21)		0 (0-14.3)	0	

% (95% CI) = 13-year incidence of reflux at follow up by history of medical condition at baseline

n = number of participants with venous reflux at follow up, (N) = number of participants with history or no history of medical condition at baseline

[a] Deep reflux only = reflux ≥ 0.5 s in CFV, FV or POP + no reflux in GSV or SSV at follow up

[b] Superficial reflux only = reflux ≥ 0.5 s in GSV or SSV + no reflux in CFV, FV or POP at follow up

[c] Combined reflux = reflux ≥ 0.5 s in CFV, FV or POP + reflux ≥ 0.5 s in GSV or SSV at follow up

*P value based on chi square test for difference in incidence of reflux in participants by history of medical conditions at baseline.

TABLE 11.3 13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS DURATION AT FOLLOW UP BY HISTORY OF MEDICAL CONDITIONS AT BASELINE (CONTINUED)

	13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS								
	DEEP REFLUX ONLY [a]			SUPERFICIAL REFLUX ONLY [b]			COMBINED REFLUX [c]		
MEDICAL CONDITION	% (95% CI)	n (N)	P value*	% (95% CI)	n (N)	P value*	% (95% CI)	n (N)	P value*
SWOLLEN LEG POST OP									
- No	2.5 (1.1-5.0)	7 (279)	0.36	8.3 (5.4-12.3)	23 (276)	0.16	1.1 (0.3-3.0)	3 (274)	0.84
- Yes	6.3 (0.3-30.8)	1 (16)		18.8 (4.8-51.0)	3 (16)		0 (0-18.7)	0 (16)	
SWOLLEN LEG PREG									
- No	2.3 (0.4-7.5)	2 (87)	0.70	10.3 (5.0-19.0)	9 (87)	0.59	0 (0-3.5)	0 (86)	0.35
- Yes	2.0 (0.1-9.9)	1 (50)		10.6 (3.9-23.6)	5 (47)		2.1 (0.1-10.5)	1 (47)	
SWOLLEN LEG OTHER									
- No	2.9 (1.2-6.0)	6 (208)	0.60	8.8 (5.4-13.6)	18 (205)	0.72	0.5 (0.1-2.4)	1 (205)	0.42
- Yes	3.1 (0.5-10.3)	2 (64)		6.3 (2.0-15.3)	4 (63)		1.6 (0.1-7.8)	1 (63)	
FRACTURED LEG									
- No	2.5 (1.1-5.0)	7 (279)	0.54	9.0 (6.0-13.1)	25 (277)	0.56	1.5 (0.5-3.5)	4 (275)	0.69
- Yes	3.6 (0.2-17.6)	1 (28)		7.4 (1.2-24.4)	2 (27)		0 (0-11.1)	0 (27	

% (95% CI) = 13-year incidence of reflux at follow up by history of medical condition at baseline

n = number of participants with venous reflux at follow up, (N) = number of participants with history or no history of medical condition at baseline

[a] Deep reflux only = reflux ≥ 0.5 s in CFV, FV or POP + no reflux in GSV or SSV at follow up

[b] Superficial reflux only = reflux ≥ 0.5 s in GSV or SSV + no reflux in CFV, FV or POP at follow up

[c] Combined reflux = reflux ≥ 0.5 s in CFV, FV or POP + reflux ≥ 0.5 s in GSV or SSV at follow up

*P value based on chi square test for difference in incidence of reflux in participants by history of medical conditions at baseline.

Swollen leg post pregnancy based on 138 women free of venous reflux at baseline

TABLE 11.4 13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS DURATION AT FOLLOW UP, BY NUMBER OF PREGNANCIES AT BASELINE

	13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS								
	0 PREGNANCIES		1-2 PREGNANCIES		3 PREGNANCIES		≥ 4 PREGNANCIES		P VALUE*
PATTERN OF REFLUX	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	
DEEP REFLUX ONLY [a]	4.3 (0.7-14.4)	2	1.4 (0.1-7.0)	1	2.6 (0.1-13.0)	1	0	0	0.32
CFV origin	2.2 (0.1-10.7)	1	0	0	0	0	0	0	
FV lower thigh	2.2 (0.1-10.7)	1	0	0	0	0	0	0	
POP lower	0	0	0	0	2.6 (0.1-13.0)	1	0	0	
POP upper + lower	0	0	1.4 (0.1-7.0)	1	0	0	0	0	
SUPERFICIAL REFLUX ONLY [b]	10.9 (4.0-24.1)	5	11.9 (5.5-22.7)	8	7.9 (2.0-21.5)	3	12.5 (3.2-34.0)	3	0.85
GSV origin	0	0	1.5 (0.1-7.4)	1	0	0	0	0	
GSV lower thigh	4.3 (0.7-14.4)	2	3.0 (0.5-9.9)	2	2.6 (0.1-13.0)	1	12.5 (3.2-34.0)	3	
SSV	2.2 (0.1-10.7)	1	0	0	2.6 (0.1-13.0)	1	0	0	
GSV origin + GSV lower thigh	2.2 (0.1-10.7)	1	3.0 (0.5-9.9)	2	0	0	0	0	
GSV lower thigh + SSV	2.2 (0.1-10.7)	1	1.5 (0.1-7.4)	1	2.6 (0.1-13.0)	1	0	0	
GSV origin + GSV lower thigh + SSV	0	0	3.0 (0.5-9.9)	2	0	0	0	0	
COMBINED REFLUX [c]	2.2 (0.1-10.7)	1	0	0	2.6 (0.1-13.0)	1	0	0	0.74
POP lower + GSV thigh	2.2 (0.1010.7)	1	0	0	0	0	0	0	
POP lower + SSV	0	0	0	0	2.6 (0.1-13.0)	1	0	0	

% (95% CI) = 13-year incidence of reflux by vein segment affected according to number of pregnancies at baseline

n = number of participants with no reflux at baseline but reflux in vein segment at follow up according to number of pregnancies at baseline

* P value based on linear trend for test for difference in incidence of venous reflux by number of pregnancies at baseline

[a] Deep reflux only = reflux ≥ 0.5s in CFV, FV or POP + no reflux in GSV or SSV at follow up, based on 179 females:

[b] Superficial reflux only = reflux ≥ 0.5s in GSV or SSV + no reflux in CFV, FV or POP at follow up, based on 175 females

[c] Combined reflux = reflux ≥ 0.5s in CFV, FV or POP + reflux ≥ 0.5s in GSV or SSV at follow up

TABLE 11.5 13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS DURATION AT FOLLOW UP BY MOBILITY AT WORK AT BASELINE

	13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS								
	DEEP REFLUX ONLY [a]			SUPERFICIAL REFLUX ONLY [b]			COMBINED REFLUX [c]		
MOBILITY AT WORK	% (95% CI)	n (N)	P value*	% (95% CI)	n (N)	P value*	% (95% CI)	n (N)	P value*
SITTING									
< 50% of the time	3.0 (1.1-6.7)	5 (166)	0.88	6.1 (3.1-10.9)	10 (164)	0.41	1.2 (0.2-4.0)	2 (164)	0.63
> 50% of the time	2.1 (0.5-5.7)	3 (142)		7.0 (3.6-12.5)	10 (142)		1.4 (0.2-4.7)	2 (140)	
STANDING									
< 50% of the time	2.8 (1.1-5.8)	6 (217)	0.56	7.0 (4.0-11.2)	15 (215)	0.13	1.4 (0.4-3.8)	3	0.65
> 50% of the time	2.2 (0.4-7.2)	2 (92)		13.2 (7.1-22.4)	12 (91)		1.1 (0.1-5.4)	1 (91)	
WALKING									
< 50% of the time	1.4 (0.3-3.7)	3 (221)	0.08	9.1 (5.7-13.8)	20 (220)	0.99	1.8 (0.6-4.4)	4 (218)	0.27
> 50% of the time	5.7 (2.1-12.7)	5 (87)		8.2 (3.6-16.3)	7 (85)		0 (0.1-3.5)	0 (80)	
HEAVY WORK									
< 50% of the time	2.7 (1.2-5.3)	7 (259)	0.62	8.6 (5.5-12.7)	22 (257)	0.44	0.8 (0.1-2.6)	2 (255)	0.12
> 50% of the time	2.0 (0.1-9.9)	1 (50)		10.2(3.7-22.6)	5 (49)		4.1 (0.7-13.5)	2 (49)	

% (95% CI) = 13-year incidence of reflux at follow up by mobility at work based on % of time spent sitting, standing, walking and lifting heavy objects

n = number of participants with venous reflux at follow up, (N) = number of participants spending <50% and >50% of time at work sitting, standing, walking and lifting heavy objects

[a] Deep reflux only = reflux ≥ 0.5 s in CFV, FV or POP + no reflux in GSV or SSV at follow up

[b] Superficial reflux only = reflux ≥ 0.5 s in GSV or SSV + no reflux in CFV, FV or POP at follow up

[c] Combined reflux = reflux ≥ 0.5 s in CFV, FV or POP + reflux ≥ 0.5 s in GSV or SSV at follow up

* P value based on chi square test for difference between incidence of venous reflux in participants according to mobility at work at baseline

TABLE 11.6 13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS DURATION AT FOLLOW UP, ACCORDING TO SMOKING STATUS AT BASELINE

	13 YEAR INCIDENCE OF REFLUX ≥ 0.5 SECONDS				
	NEVER SMOKED (N = 163)		EVER SMOKED (N = 184)		P VALUE*
PATTERN OF REFLUX	% (95% CI)	n	% (95% CI)	n	
DEEP REFLUX ONLY [a]	3.1 (1.1-6.8)	5	1.2 (0.06-5.9)	1	0.42
CFV origin	0.6 (0.03-3.0)	1	0	0	
POP lower	1.2 (0.2-4.0)	2	0	0	
POP upper + lower	1.2 (0.2-4.0)	2	1.2 (0.06-5.9)	1	
SUPERFICIAL REFLUX ONLY [b]	9.9 (5.9-15.7)	16	9.6 (4.5-18.3)	8	0.79
GSV origin	0	0	2.4 (0.4-8.4)	2	
GSV lower thigh	2.5 (0.8-6.0)	4	4.8 (1.5-11.6)	4	
SSV	1.9 (0.5-5.0)	3	0	0	
GSV origin + GSV lower thigh	3.1 (1.1-6.8)	5	0	0	
GSV origin + SSV	0	0	0	0	
GSV lower thigh + SSV	1.2 (0.2-4.1)	2	1.2 (0.06-5.9)	1	
GSV origin + lower thigh + SSV	1.2 (0.2-4.1)	2	1.2 (0.06-5.9)	1	
COMBINED REFLUX [c]	0.6 (0.03-3.1)	1	2.4 (0.4-8.1)	2	0.65
POP lower + SSV	0	0	1.2 (0.06-6.0)	1	
POP lower + GSV lower thigh + SSV	0.6 (0.03-3.1)	1	0	0	
CFV + POP upper + lower + GSV origin + GSV lower thigh	0	0	1.2 (0.06-6.0)	1	

% (95% CI) = 13-year incidence of reflux by vein segment affected according to smoking status at baseline

n = number of participants with no reflux at baseline but reflux in vein segment at follow up according to smoking status at baseline

[a] Deep reflux only = reflux ≥ 0.5 s in CFV, FV or POP + no reflux in GSV or SSV at follow up, based on 247 participants: never smoked (163) ever smoked (84)

[b] Superficial reflux only = reflux ≥ 0.5s in GSV or SSV + no reflux in CFV, FV or POP at follow up, based on 245 participants: never smoked (162), ever smoked (83)

[c] Combined reflux = reflux ≥ 0.5s in CFV, FV or POP + reflux ≥ 0.5s in GSV or SSV at follow up, based on 243 participants: never smoked , ever smoked

*P value based on test for chi squared test for difference in incidence of venous reflux in any leg at follow up according to smoking status at baseline

CHAPTER 12: DISCUSSION

12.1 CHAPTER OUTLINE

The Edinburgh Vein Study Follow up is one of the few large scale population-based cohort studies recently conducted to investigate the incidence of C2 varicose veins, C3-C6 chronic venous insufficiency, venous reflux ≥ 0.5 seconds duration and associated risk factors. This chapter begins by discussing the recruitment process, the response achieved and the representativeness of the study sample. The limitations of the study, including the diagnosis of CVD and measurement of reflux, are presented. It then proceeds to explore the main findings of the follow up study including the prevalence of CVD, incidence of C2 varicose veins and C3-C6 CVI and reflux. Risk factors measured in this study are discussed and compared with results from other studies. The public health implications of the results of this study are then considered. Finally the conclusions of the study are stated and recommendations and plans for future research made.

12.2 RECRUITMENT AND RESPONSE

12.2.1 Recruitment

The key process in recruitment was to obtain current contact details for all surviving baseline participants. This was done through Practitioner Services Division (PSD), a division of NHS National Services Scotland (NHS NSS). PSD act as data custodians for the Community Health Index (CHI), a database in which every patient registered in Scotland is allocated a unique identifying number. CHI is linked to the National Health Services Central Register (NHSCR), which contains details on every patient born in Scotland. For patients who have moved away from Scotland but remain in the UK, the NHSCR identifies the health authority where that individual is registered with a GP. The CHI and NHSCR are updated and synchronised every week and therefore it was the most effective way to retrieve up-to-date contact details for all participants.

The initial search of CHI retrieved addresses for all surviving baseline participants residing in Scotland. However, individuals may have moved house but not yet registered with another general practitioner located in the catchment area of their new address. In such cases, CHI would not have updated and the address retrieved by the search would have been inaccurate. It was assumed that any individual who did not respond to the study invitation could potentially have moved address. For these individuals, addresses provided by CHI were checked against GP practice registers. However, if the individual had not registered with another GP, the current practice would have been unaware that the patient had changed address. There was no way to overcome this and therefore it was accepted that some individuals would probably not receive their study invitation.

For individuals not living in Scotland but elsewhere in the UK, only the health authority where the individual was registered with a general practitioner was provided. Due to confidentiality regulations, health authorities would not release the individuals' contact details but agreed to send the study invitation to them. This method did result in some individuals travelling from England to take part in the follow up study but it was not as fruitful as hoped. With no contact details and reliant upon a third party passing on information, it was impossible to determine if these individuals received a study invitation. However, this was the only way in which individuals living outside Scotland could be contacted.

Intensive efforts were made to try to recruit as many people as possible to the follow up study. An administrative assistant was employed to trace individuals and send study invitations. Individuals were sent two invitation letters before attempts were made to contact them by telephone, made at different times of the day to try to improve response. If the individual could still not be reached, contact was made with the general practice to check if they were still registered as a patient there. A second search of CHI was performed in case the individual's details had changed since the first search. To try to maximise participation in the follow up study, appointment times from 7.30 am to 3.30 pm were offered to participants. Where there was demand, evening clinics were arranged to accommodate individuals who could not attend during the day. Participants were reimbursed travel costs and recompensed for loss of earnings through time taken off work.

With any long term follow up study, it is important to keep good relations with the study community. Written reminders have been proven to increase the response rate in cohort studies (Edwards 2002, Ronckers 2004). Therefore, at year 6 of the 13-year follow up, newsletters were sent to all baseline participants outlining the key results in a language that the lay participant would understand. It was hoped that, through highlighting the importance of the research and acting as a prompt for the follow up study, the newsletter would maximise participation at a later date.

12.2.2 Response

Individuals were classified into 5 groups based on response. "Participants" were those who agreed to take part in the study and underwent a follow up examination. "Refusals" comprised individuals who replied declining to participate in the study. "Withdrawals" were those who initially agreed to take part in the follow up study but subsequently failed to attend their appointment. "No response" comprised any individual who did not reply to the study invitation and could not be contacted by telephone. This group included those who may have moved address and also those who did not respond to the study invitation passed on by the heath authority. Assuming that the address from CHI was accurate and that the health authority passed on the invitation, it was presumed that these individuals received the invite to take part but chose not to respond. However with no contact details for these individuals, this cannot be determined. Finally, "unable to trace" were cases where the health authority did not confirm whether the individual was registered there and so it was known that they did not receive the invitation to take part in the follow up.

The response rate at follow up was based on the number of participants who were eligible to take part. Individuals who had died or emigrated since taking part at baseline were not included. The sample size calculation at baseline assumed that 50% of the cross-sectional study participants would be followed up. Therefore, the response rate of 60.4% at follow up was adequate to measure the incidence of varicose veins and CVI with the required precision. Given the length of the follow up and the current climate and sceptical attitudes of the population to participating in research, the response rate achieved was deemed satisfactory.

The response rate of 60.4% was higher than the 53.8% response achieved at the cross-sectional study at baseline. However a higher response to follow up would be expected as participants were known volunteers who had previously been examined at the baseline study. Another reason for the higher response to follow up could be that those who took part at baseline, particularly those with C2 varicose veins or C3-C6 CVI may have been eager to discover if their disease had changed over the 13 years. The follow up appointment comprised of a duplex ultrasound scan to check for venous reflux, a procedure not routinely conducted if an individual consults their GP about CVD. Therefore the individual may have felt that this was a rare opportunity to have a thorough examination of their leg veins. The fact that the results of the examination were sent to participants' GPs may have provided a further incentive to take part.

Individuals who refused to take part in the study (n=172) were sent a questionnaire to determine their venous disease status and ascertain the reason for their refusal. Of the 98 who completed the questionnaire, 58% stated that the reason they did not want to participate was that they did not have venous disease so they felt research was not relevant to them. The information sheet sent with the letter of invitation highlighted the importance of the research even in those without venous disease. Lack of time was the second most common reason for refusing to take part in the follow up study (22%). Early morning and evening appointments were offered to accommodate individuals who could not attend during working hours.

12.3 REPRESENTATIVENESS OF THE STUDY SAMPLE

12.3.1 Study population

Participants in the follow up study were from higher social classes than non-participants. There is a commonly accepted observation that people who take part in research studies tend to be more affluent. The relationship between social class and health has many influencing factors but generally speaking those in lower social classes eat a poorer diet, exercise less and are more likely to smoke than those in higher social classes. Consequently they may be less inclined to take part in a research study into a disease. However, with no evidence that neither social class nor mobility at work are associated with the development of C2 varicose veins or C3-C6 CVI, the higher proportion of non-manual workers should not have distorted the results.

Follow up study participants were also more likely to be non-smokers than non-participants. The Tampere study also reported that those lost to follow up were more likely to be smokers (Ahti 2009). Smokers take less interest in their health and would possibly be less likely to participate in a research study on venous disease. Furthermore, smoking is associated with social class. The prevalence of smoking is higher in manual compared to non-manual socioeconomic groups (National Institute for Clinical Excellence 2013). As the follow up study sample contained a higher proportion of non-manual workers, it would be expected that a higher proportion of study participants would be non-smokers. However as there was no association between smoking and CVD in this study or indeed other studies, the higher proportion of non-smokers in this sample would not have affected the results of the study.

Follow up participants reported previous varicose vein surgery more often than non-participants. This would be expected as individuals with surgically treated veins would have an increased incentive to take part. Interestingly, family history of CVD at baseline did not affect whether an individual took part in the follow up study. It was thought that individuals with a history of venous disease in their family would have been more likely to participate in the study. However, participants and non-participants reported a similar prevalence of family history at baseline. Family history may have changed during follow up and relatives may have developed new venous disease. This could have provided an added incentive for taking part in the study. On the other hand, those with no change in family history may have been less inclined to take part. There was no way to clarify this theory. Attempts were made to contact the "refusals" and "withdrawals" to determine family history. However, as 22% of eligible participants did not respond to study invitations or phone calls, family history at follow up could not be determined in a large proportion of non-participants.

Other risk factors at baseline such as obesity, history of medical conditions and pregnancy were equally distributed between participants and non-participants, indicating that there was no significant difference in proposed risk between those who did and did not take part in the follow up study.

There were no significant differences between the baseline prevalence of C2 varicose veins and C3-C6 CVI in participants and non-participants of the follow up study. Furthermore, the prevalence of venous reflux ≥ 0.5 seconds duration at baseline was similar between the two groups. With the exception of swollen legs, participants and non-participants did not differ in the reported frequency of symptoms of CVD at baseline. These findings suggest that the final study sample was representative of the baseline study population with regards to CVD.

12.3.2 Population of Edinburgh

An important issue in any study is whether the study participants are representative of the wider population. Follow up participants were compared to the population of Edinburgh in terms of age, sex and social class. Participants were slightly older than the population of Edinburgh. Given that the prevalence of CVD increases with age, the final study sample would be likely to include a higher proportion of people with CVD than in the adult population of Edinburgh.

The proportion of women in the study sample was 4% higher than the proportion of women living in Edinburgh. Some studies have shown an increased prevalence of varicose veins in women compared to men but the results are variable. Conversely, at the baseline phase of the study, the prevalence was higher in men. However as the proportion of women in the study was only marginally higher than the general population, it was unlikely to affect the representativeness of the study sample. Participants in the follow up study tended to be less deprived than the population of the City of Edinburgh. However, there is no evidence that CVD is linked to social class and so the inclusion of fewer deprived individuals is unlikely to affect the results of the study.

12.4 LIMITATIONS OF THE STUDY

12.4.1 Loss to follow up

The response rate achieved at follow up in the Edinburgh Vein Study was 60%. Strenuous efforts were undertaken to maximise participation but despite these, 40% of the study population did take part in the follow up study because they refused, did not respond to the invitation, withdrew from the study or were unable to trace. Loss to follow up is a common and inevitable problem in prospective cohort studies. It is an important problem as non-responders may be different from those who participate, thus introducing bias and threatening the validity of the study results. Various comparisons were made between participants and non-participants to check the representativeness of the study sample to the study population. Comparisons included age, sex, prevalence of CVD and reflux, previous treatment and family history of CVD and other risk factors such as BMI, pregnancy, smoking and medical history.

Results of these comparisons showed that participants in the follow up study were older than non-participants (47 years and 42 years respectively). While the mean difference in age was small, it was statistically significant ($p<0.001$) and given that the incidence and prevalence of both varicose veins and CVI have been shown to increase with age, it is likely that the final study sample may contain a higher proportion of people with venous disease.

Participants in the follow up study were more likely to have had treatment for varicose veins than non-participants. Consequently it would be expected that participants may have had more symptoms of varicose veins at baseline. However this was not the case. There were no significant differences between participants and non-participants in terms of the prevalence of either C2 varicose veins or C3-C6 CVI at baseline. Some participants free from disease at baseline may have developed varicose veins during the 13 years, thus providing an incentive to take part in the follow up study. While this could account for the lack of statistical difference in prevalence between participants and non-participants, it does not account for the significantly higher treatment rate at baseline between the two groups. It is important to note that when comparing the prevalence of varicose veins between participants and non-participants, this measure is at baseline and does not take into account changes during the follow up. Attempts were made to measure varicose veins at follow up by sending questionnaires to those who refused to take part in (n=172), did not respond (n=321) or withdrew (n=69) from the follow up study. Of the 562 non-participants who were sent a questionnaire, only 98 (17%) completed it. With the varicose vein status unknown in the majority of non-participants (83%) it cannot be ruled out that the final study sample may contain a higher proportion of people with varicose veins than the study population.

12.4.2 Classification of chronic venous disease

At baseline, the Basle system was used to classify CVD as it is was the most widely accepted method at that time. However, during the follow up the CEAP system was developed and has since become the gold standard method. To ensure direct comparison between results at baseline and follow up, and to permit comparisons with other studies that have used the CEAP classification, both the Basle and CEAP were used at follow up. Despite the use of a standardized classification system to diagnose CVD, there were issues around observer error and reliability, which will now be addressed.

Variation between classification of baseline and follow up observers

Given that different observers classified CVD at the two stages of the study, it was imperative to check for variations between observers at baseline and follow up. A sample of 100 baseline participants was chosen by selecting every 15th participant from the study list. Photographs of this sample were analysed by observers at follow up. Observers classified CVD independently and were blinded to the classification awarded by the baseline observers. Results of agreement suggested that the variability between observers was tolerable.

Classification at examination and using photographs

Classification of CVD was based predominantly on examination of the participant and supported with photographic evidence, where available. Comparison of the two methods identified four discrepancies. C1 telangiectases and reticular veins and C3 corona phlebectatica were classified at a higher grade based on photographic evidence. Conversely, C2 varicose veins were classified at a higher grade upon examination. However, photographic evidence was only available on 77% of follow up participants. Although the preference was to use examination rather than photographic data because the former was more complete, the results of the comparison between the examination and photographic methods indicated that amendments would improve the accuracy of the data to be included in the statistical analysis, the observer variability and the validity of the study results. Therefore classification of C1 telangiectases and reticular veins and C3 corona phlebectatica were based on photographic evidence, where available.

Inter-observer variability at follow up

Despite regular quality control measures during data collection, a limitation of this study was some degree of inconsistency between observers in the classification of disease on clinical examination. Analysis showed that one observer reported fewer mild C2 varicose veins at examination. However, when this observer's classification based on photographic evidence was compared to the other observers, no significant difference in the prevalence of mild C2 veins was found, suggesting an under-reporting at examination. As a result, amendments were made so that for participants examined by this observer, a grade 0 C2 vein at examination was changed to a grade 1 (mild), if that was the finding on the photographic evidence. Analysis also highlighted an over-

reporting of C4 venous eczema at examination by another observer. Consequently, an amendment was made so that the classification of C4 eczema was based on photographic evidence for this observer. Photographs were taken at both stages of the study to ensure that there was supporting evidence available on the classification of disease. Since photographs were not available for all participants, they could not be substituted completely for clinical examination data but were used where feasible to correct known misclassifications. It was considered that this approach provided the most valid assessment of venous disease, particularly as the appraisal of photographs were made independently by two observers, blind to the results of the clinical examination.

Intra-observer variability at follow up

Forty-nine participants had CVD classified by the same observer who completed the first classification. A minimum period of 12 weeks was allowed between appointments so that the observer would be unaware of the classification at the first examination. However the sample was not large enough to identify discrepancies during the study. Only when comparing prevalence between observers at the end of the study was it clear that there was an under-reporting of C2 varicose veins upon examination by one observer. This is not uncommon in epidemiological studies where observers "drift" over time. Fortunately photographs provided back up to highlight and investigate such problems. As there were known intra observer errors, it was considered that amending the errors based on the photographic evidence would result in a more accurate estimate of CVD.

12.4.3 Measurement of venous reflux

While duplex scanning has become the method of choice for investigation of venous reflux, debate surrounding the optimum position and technique still exists. Currently there is no systematic consensus agreement on how duplex ultrasound for CVD is best performed. Most observers (Coleridge-Smith 2006, Labropoulos 2005, Nicolaides 2000) recommend examining the patient in a standing position but others have suggested that a reverse Trendelenburg is also adequate (Bonfield 2012). Reflux > 0.5 seconds is generally used but a definitive cut off point for all segments has not been agreed. Labropoulos et al. suggest a cut-off point of > 1 second for popliteal segments (Labropoulos 2003). Furthermore while the pneumatic cuff is the most reproducible method to elicit reflux, the Valsalva manoeuver is recommended for measuring incompetence in the saphenofemoral junction (Coleridge-Smith 2006).

Ideally duplex ultrasound would have been combined with a global measure of venous function of the limb such as plethysmography. This combination has been deemed to be the most accurate means of measuring reflux (Coleridge-Smith 2006). However, as the study examination lasted an hour, it was felt that asking participants to extend their appointment further would be unacceptable and could risk lowering the response rate.

To ensure that the ultrasound scans were performed in a standardised manner, a protocol was designed detailing the technique for measuring reflux in specific vein segments [Appendix 15]. The four observers at follow up were initially trained together by experienced vascular scientists and a consultant radiologist. All observers underwent a practical exam, in which they were required to perform a duplex ultrasound on a volunteer, while being assessed by a vascular scientist. Only when observers passed this exam were they deemed competent enough to conduct ultrasound scans in the study.

Every participant was examined on a table tilted to an angle of 45 degrees. An automated rapid inflation/deflation cuff was used to elicit reflux as it provides a standard stimulus to evaluate reflux parameters (Labropoulos 2005). The calf veins were not examined at baseline and therefore were not examined at follow up. It has been shown that calf veins have a role in popliteal reflux (Allan 2000). However, with no reflux measures for the calf veins at baseline, data at follow up would be of limited use. While this may leave some questions unanswered, it was considered that duplex scanning of the calf and perforator veins would be difficult for the research team to learn and of doubtful accuracy (Evans 2002).

Inter-observer variability at follow up

Inter-observer agreement ranged from 83-98% for measures of reflux in the deep veins and 79-95% for the superficial veins. The poorest agreement was for reflux in the GSV in the lower third of the thigh. This segment is acknowledged as difficult to measure due to the anatomical variations around the knee (Cavezzi 2006). Furthermore, according to a consensus document on duplex ultrasound for the investigation of CVD, the GSV in the thigh is often "accompanied by parallel veins of different length that are so large that they may be confused with the GSV itself or considered to be the double saphenous veins" (Cavezzi 2006). Inter observer agreement was lower for the SSV. Observers at baseline also had difficulty in measuring reflux in this segment. Over a quarter (26%) of baseline participants were recorded as having missing reflux SSV measurements, as observers were not confident that they had correctly identified the vein. The SSV is prone to anatomical variations including a missing vein or a double or triple duplicated vein. The SSV was a difficult segment to measure at both stages of the study and so the results must be interpreted with caution.

Intra-observer variability at follow up

Intra-observer variability ranged from 70-100%, which indicates that each observer achieved similar reflux results at two different ultrasound examinations. The agreement was poorest for the GSV upper and lower calf. As these vein segments are located distally, the pneumatic compression device could not be used. Rather, foot compressions were performed where the observer squeezed the foot to initiate blood flow. Unlike the pneumatic calf compression, which was set at a standard pressure, the pressure applied to the foot may have varied with each compression. This variability may have accounted for the lower level of agreement for these vein segments.

Cut-off point for venous reflux

At baseline and follow up, abnormal venous reflux was defined as reflux ≥ 0.5 seconds duration. However, there is debate over what constitutes significant reflux. While some authors use duration of reverse flow of greater than 0.5 seconds as a definition for significant reflux, others argue that this definition would include individuals with normally functioning veins, and use a value of greater than 1 second duration, particularly for the popliteal veins (Labropoulos 2003). Determining which cut-off point to use is a complex issue. Using reflux duration ≥ 0.5 decreases the specificity, and could result in a larger proportion of normal veins determined to be incompetent, while using a reflux duration > 1.0 second decreases the sensitivity, and risks diagnosing a larger proportion of incompetent veins as normal (Evans 2002).

It was intended to analyse the relationship between the duration of reflux ≥ 0.5 seconds and > 1.0 second at baseline and the incidence of C2 varicose veins and C3-C6 CVI at follow up. However the number of participants who developed any reflux ≥ 0.5 seconds at follow up was too small for the analysis to provide any meaningful results. Severity of reflux is thought to be an important factor in the progression of CVD to and this will be analysed in the part of the study looking at deterioration of clinical disease.

12.4.4 Limited power

One of the limitations of this study is that although the follow up study sample of 880 participants exceeded the 750 assumed in the sample size calculation, when incident cases were split into subgroups for analysis the numbers were small, thus limiting the power of the study to detect true differences. This was a particular problem when analysing venous reflux. Although the overall incidence of venous reflux was 12%, when split according to vein segment affected, the numbers with reflux in certain segments were very small. Consequently important risk factors may not have been identified. Furthermore the true association between the prevalence of venous reflux at baseline and the incidence of varicose veins at follow up may not have been detected. This was also the case for pregnancy and the incidence of varicose veins where data identified it as a risk factor but the association was not statistically significant due to small numbers. Only 47 of the 334 women in the study had one or more pregnancies at baseline. When split further to test the trend for number of pregnancies, the subgroups became smaller still and while a linear trend was noted, the trend was not statistically significant ($p=0.42$). Therefore, in this study non-significant results must not be discounted but interpreted with caution. It is imperative to look at the number of cases on whom associations are being tested and consider that that the lack of a statistical result may be due to the small numbers limiting the power of the study to detect true associations.

12.4.5 Multiple testing

Data in this study underwent multiple statistical testing. One problem of performing multiple tests is that inevitably there will be type I errors. Type I errors occur when the true null hypothesis is incorrectly rejected. Consequently an association is observed when in truth there is none (false positive). Methods to adjust for type I errors include the Bonferroni correction. However it is a conservative measure and increases the probability of producing false negatives, where there is an effect but it is not identified as statistically significant. Multiple test correction was not performed in this study and therefore it should be acknowledged that some of the statistically significant results may not be true associations but occurred by chance alone. As such the results should be interpreted with caution.

12.5 PREVALENCE OF C1-C6 CHRONIC VENOUS DISEASE AT FOLLOW UP

The prevalence of C2 varicose veins increased from 36.9% at baseline to 39.2% at follow up. The proportion of mild cases decreased but the proportion of moderate and severe C2 varices increased. As the severity was based on the highest grade, this finding suggests that those with mild varicose veins at baseline deteriorated to moderate or severe varicose veins over the 13 years. Clinical manifestations of C3-C6 CVI also increased during follow up, particularly mild forms such as C3 corona phlebectatica (16.7%) and C4a pigmentation (5.5%). Given that CVD represents a spectrum of conditions of increasing severity associated with age, it would be expected that the prevalence of C3-C6 CVI would increase as some individuals with C2 varicose veins at baseline would have deteriorated during the 13 years. Severe CVI including C5 healed and C6 active venous ulceration remained uncommon with a prevalence of only 0.8% at follow up.

Overall, the prevalence of C1 telangiectases decreased from 92% at baseline to 85% at follow up while the prevalence of C1 reticular veins decreased further from 90% to 70% over the 13 year period. While the prevalence of moderate and severe C1 veins increased during the 13 years, the decrease in mild telangiectases and reticular veins accounted for the lower prevalence observed at follow up. The increase in the proportion of moderate and severe veins suggests some progression from baseline. However, given that the prevalence of C2 varicose veins has been associated with age, it would have been expected that the prevalence of these conditions would also have increased over the 13-year follow up.

It was postulated that varicose vein surgery may have improved the appearance of mild C1 veins. To test this theory, participants who had surgery between baseline and follow up examinations were excluded. However this had little effect on the prevalence. Only 6.6% of the follow up participants reported using compression stockings which could not account for the improvement in mild C1 veins. A possible explanation could be that mild C1 telangiectases and reticular veins were misclassified either at baseline or follow up. The prevalence of both these conditions was estimated at over 90% at baseline. Estimates from other studies suggest that the prevalence is approximately 80% (Evans 1994). Therefore it is possible that C1 mild veins were over reported at baseline. Alternatively, observers at follow up could have under reported the prevalence of these conditions. Results suggested that the agreement between the observers at baseline and follow up were tolerable. Clearly some observer variability existed, as it would be unlikely that a mild C1 reticular vein would simply disappear over 13 years.

12.5.1 Age differences

At follow up, the prevalence of both C2 varicose veins and C3-C6 CVI increased linearly with age, regardless of sex. Other evidence suggests that, on balance, the prevalence of CVD increases with age (Abramson 1981, Arnoldi 1958, Beaglehole 1975, Canonico 1998, Coon 1973, Criqui 2003, Evans 1999, Franks 1992, Guberan 1973, Komsuoglu 1994, Maffei 1986, Mekky 1969, Sisto 1995, Stanhope 1975, Widmer 1978). It has been postulated that ageing is associated with a change in size and elasticity of the venous wall, thus predisposing to varicose veins (Clarke 1992).

12.5.2 Sex differences

C1 telangiectases were more prevalent in women (90.2%) than in men (79%). The prevalence of C2 varicose veins was 40.0% (95% CI 35.3-44.5) in men compared to 38.6 (95% 34.4-42.9) in women (p=0.67) This was an interesting finding as baseline results suggested a statistically significantly higher prevalence of C2 varicose veins in men (39.7%) compared to women (32.2%). Evidence from previous studies of varicose veins suggested a higher prevalence in women (Abramson 1981, Beaglehole 1975, Coon 1973, Criqui 2003, Franks 1992, Komsuoglu 1994, Kontosic 2000, Laurikka 1993, Leipnitz 1989, Maffei 1986, Novo 1988, Sisto 1995) although the magnitude of difference varied between studies (See Chapter 2, Tables 2.1 and 2.2). The prevalence of C3-C6 CVI was similar between men and women at follow up (p>0.05). At baseline, the prevalence of CVI was similar between men and women, suggesting that during follow up, venous disease developed at a similar rate between sexes. However the small number of cases with CVI could be obscuring the true differences.

12.6 PREVALENCE OF VENOUS REFLUX AT FOLLOW UP

At baseline, the prevalence of deep venous reflux only (without superficial reflux) was significantly higher in men (25.2%, 95% CI 20.6-30.6) than in women (14.4%, 95% CI 11.3-18.1) ($p<0.001$). Conversely superficial reflux (without deep reflux) was more common in women (20.3%, 95% CI 16.3-25.1) than in men 11.6, (95% CI 8.4-15.6) ($p=0.02$). The prevalence of combined deep and superficial reflux did not differ between genders (20.0%, 95% CI 15.8-25.0 in men and 16.5%, 95% CI 37.1-58.0 in women ($p=0.22$). At follow up, men no longer had a statistically higher prevalence of deep venous reflux ($p=0.75$). However, the trend for a higher prevalence of isolated superficial venous reflux in women remained ($p<0.001$).

The Bochum Study also found that women had a significantly higher prevalence of superficial reflux (Schultz-Ehrenburg 1992). While it has been hypothesized that men may have larger deep veins which take longer for the valves to close completely (Allan 2000), there is no known anatomical reason why women should have a higher prevalence of superficial reflux than men.

Analysis of the data showed that individuals with isolated superficial reflux at baseline were more likely to have C2 varicose veins at follow up. Moreover, those with combined deep and superficial reflux were at an even greater risk of developing C2 varicose veins at follow up. In particular, reflux in the GSV at the origin and in the lower third of the thigh were the key vein segments identified as contributing to the development of C2 varicose veins. This is supported by Labropoulos et al. who identified that above knee GSV reflux was the contributing factor to the prevalence of varicose veins without skin changes (Labropoulos 1997). As the majority of new C2 veins were classified as mild, it was not possible to conduct an analysis on the effect of reflux on the severity of C2 veins. However, results on the prevalence at baseline suggested a higher prevalence of reflux in participants with more severe varices.

Deep venous reflux appeared to be associated with the development of C3-C6 CVI. This association did not reach statistical significance, possibly due to the small number of participants developing CVI during follow up. Despite the lack of statistical association, the trend cannot be ignored, particularly when other studies have shown deep venous reflux to be an important cause of venous ulceration (MacEnroe 1988, Raju 1983). Furthermore it has been shown that that popliteal vein reflux reduces the healing of chronic venous ulcers (Brittenden 1998).

12.7 INCIDENCE OF C2 VARICOSE VEINS AND C3-C6 CVI AT FOLLOW UP

Results from the Edinburgh Vein Study Follow Up suggest that approximately 1.4% of the general population will develop C2 varicose veins each year, the majority of which are mild. The incidence reported in this study is lower than in the Framingham Study, a longitudinal study with a follow up every 2 years over a 16-year period in the USA (Brand 1988). The annual incidence of varicose veins was 4.6%. However the Framingham Study was conducted before the introduction of a standard classification system. Although varicose veins were defined as "the presence of distended and tortuous veins, clearly visible in the lower limbs with the subject standing", the lack of precise and reliable criteria for diagnosis is a drawback in any epidemiological study. In the Bonn Vein Study II, where 1,978 of 3,072 participants were re-examined after a 6.6-year follow up, the incidence of varicose veins was 2.1% per year (Rabe 2010). However the methods of derivation of incidence were not reported and it is not clear if the incident cases in this study were free of varicose veins at baseline. The Tampere Study reported an incidence of 1.3% per year (Mäkivaara 2004). However varicose veins were based on self-diagnosis via a questionnaire and only 2.4% of the study sample underwent physical examination to confirm the diagnosis. The Bochum Study examined school children on three occasions over an eight-year period and used the CEAP classification system to diagnose varicose veins (Schultz-Ehrenburg 1992) None of the children aged 10-12 years had varicose veins at the first examination. The incidence was 1.7% at age 14-16 years and 3.3% by age 18-20 years. However given that the prevalence of varicose veins is strongly associated with age, it would be expected that the incidence of varicose veins in children as young as 10-16 years would be low and not comparable with an adult population.

The annual incidence rate of CVI in the Edinburgh Vein Study Follow Up was 0.7%, 0.4% alone and 0.3% with combined development of C2 veins. The Bonn Vein Study however, found a much higher incidence rate of 2.0% per year (Rabe 2010). Again the calculation of incidence in the Bonn Vein Study II is questioned. Results seem to suggest that new cases of CVI at follow up may have had a less severe class of CVI at baseline. If this is the case then the results reported in this study are not real incidence but are actually rates of progression of disease When considering the incidence of CVI, it is important to emphasise the difference between the true incidence of CVI and natural progression of disease. The CEAP classification system represents a range of symptoms which increase in severity from C1-C6 classes. C2 varicose veins, if left untreated, can lead to more severe symptoms of CVI. As such, when an individual with C2 varices develops symptoms of CVI, it is deemed to be progression of venous disease. In the Edinburgh Vein Study the incidence of CVI was based on the number of participants with no C2 varices or CVI at baseline. Consequently participants with C2 varicose veins at baseline and C3-C6 CVI at follow up were not included as incident cases of CVI. The incidence was calculated in this way as such participants are not true incident cases but rather cases where existing venous disease has progressed to more severe symptoms.

When conducting a prospective cohort study to determine the incidence of varicose veins or CVI, it is important to consider that participants free from these conditions at the initial examination, may have developed symptoms and had subsequent treatment (surgery or sclerotherapy) during the follow up period. Consequently these participants may have had no evidence of C2-C6 disease at the follow up examination and therefore would not be included as incident cases. However, in the Edinburgh Vein Study, the questionnaire enquired about treatment for varicose veins including the type and year of procedure. Therefore, any participant free from disease at baseline who had venous surgery between baseline and follow up could be identified and included as an incident case. Of the 555 participants with no C2-C6 disease at baseline only 2 had surgery during the 13 year follow up and both of these participants had signs of C2 varicose veins at the follow up examination. Therefore it is considered that the incidence calculated in this study is the true incidence of C2 varicose veins and C3- C6 CVI. Other studies on incidence of varicose veins and CVI do not address this problem and therefore the incidence reported may not actually be the true incidence of disease (Brand 1988, Mäkivaara 2004, Rabe 2010, Schultz-Ehrenburg 1992)

12.7.1 Age differences

Results of this study indicate that the incidence of C2 varicose veins and C3-C6 CVI increases significantly with age. After adjusting for sex, participants aged 45-54 years at baseline were 2.6 times more likely to develop C2 varicose vein at follow up 13 years later than those aged 18-24 years. The odds were higher still in those aged 55-64 years (OR 3.2, 95% CI 1.6-6.4) compared to 18-24 year olds. For C3-C6 CVI the risk was approximately 2 fold in those aged 35-44 years, 7 fold in those aged 45-54 years and 9 fold in those aged 55-64 years at baseline compared to 18-24 year olds. The

Edinburgh Vein Study is the first to produce convincing evidence that the risk of acquiring both C2 varicose veins and C3-C6 CVI increases with age, a finding which would be expected in a chronic degenerative condition. These results are in keeping with the Bochum Study, where incidence of varicose veins also increased with age (Schultz-Ehrenburg 1992). However, it should be noted that participants in that study were school children aged 10-12 years at baseline, who were followed up over a 20 year period. In the Framingham Study, the incidence of varicose veins did not increase significantly with age (Brand 1988).

12.7.2 Sex differences

Results from the Edinburgh Vein Study suggest that the incidence of C2 varicose veins is similar between men and women. The age-adjusted 13 year incidence was 15.2% (95% CI 10.4-20.0) and 17.4% (95% CI 13.1-21.7) (p=0.72). There were also no observed sex differences in the incidence of C3-C6 CVI between men and women. The 13 year incidences were 10.7% (95% CI 7.2-15.5) and 8.1% (95% CI 5.7-11.6) in men and women respectively (p=0.32). These findings concur with the Bonn Vein Study II, which also found no gender difference (Rabe 2010). Evidence from other studies indicates a higher incidence in women. The Framingham Study reported annual rates of 2.6% in women and 1.9% in men (Brand 1988), while the Tampere Varicose Vein Study reported rates of 19.2/1000 person-years and 8.5/1000 person-years in women and men respectively (Laurikka 2002). However, the Tampere Study obtained information on CVD via postal questionnaire and may have had a biased response by gender. The Bochum Study found no significant gender differences but only 136 participants were followed up for the full duration of the study (Schultz-Ehrenburg 1992).

12.8 INCIDENCE OF VENOUS REFLUX AT FOLLOW UP

The 13 year incidence of venous reflux ≥ 0.5 seconds duration was 12.7%, 8.8% in the superficial system only, 2.6% in the deep system only and 1.3% in both the deep and superficial systems. The GSV was the most common vein to develop reflux with a 13 year incidence of 4.6% (95% CI 2.6-7.5), 3.9% (95% CI 2.1-6.7) and 0.3% (95% CI 0.02-1.6) in the right, left and both legs respectively.

The incidence of venous reflux did not differ by gender and was not associated with age either for individual vein segments or for the whole venous system. It is interesting to note that age was a significant risk factor for the development of C2 varicose veins and C3-C6 CVI but not for the development of venous reflux.

12.9 RISK FACTORS FOR C2 VARICOSE VEINS, C3-C6 CVI AND VENOUS REFLUX

12.9.1 Body mass index

In this study, increased body mass index was not associated with the incidence of C2 varicose veins (p=0.43) or venous reflux ≥ 0.5 s duration (p>0.50). However, it was a significant risk factor for the development of C3-C6 CVI (p trend<0.001). Participants who were overweight at baseline were 1.3 (95% CI 1.1-1.6) times more likely to have C3-C6 CVI at follow up. The risk in those who were obese was higher still at 4.5 (95% CI 3.3-6.9). Our findings concur with the Bonn Vein Study II, where obese participants had a significantly higher risk of developing oedema and skin changes associated with CVI (Rabe 2010). The Framingham Study found that obesity was significantly associated with increased incidence of varicose veins in women but not in men (Brand 1988). Obesity has also been associated with the prevalence of CVI. A case-control

study in New Zealand found that the prevalence of CVI was significantly higher in obese patients compared to non-obese, after adjusting for age, previous history of DVT, prevalence of deep venous reflux and other risk factors (van Rij 2008).

Evidence on the association of obesity and the prevalence of C2 varices is conflicting. Several studies found an association between obesity and varicose veins while others did not. Results indicate that obesity may be a significant risk factor in women only (Brand 1988, Iannuzzi 2002, Lee 2003, Widmer 1978). However, in the Basle (Widmer 1978) and Framingham (Brand 1988) studies, the associations were not significant after adjusting for age. Furthermore, studies did not adjust for parity. Given that parous women tend to have a higher body weight than nulliparous women, it is likely that this could act as a confounding factor in the association between obesity and the prevalence of C2 varices.

It is unlikely that obesity could be a risk factor for one sex but not for the other. However, an important question is whether obesity is a primary risk factor for CVD or whether it just accelerates the development or severity of disease. Abdominal pressures are increased in obese patients and it has been hypothesized that this could impede venous flow from the legs, thus causing reflux (Wall 2011). This follow up study showed no significant association between obesity and the incidence of venous reflux ≥ 0.5 seconds duration. However, the sample of participants who developed reflux was too small to draw any meaningful conclusions from. Further evidence is required to clarify the effect of obesity on the development of C2 varicose veins, C3-C6 CVI and venous reflux.

12.9.2 Family history

Results from this follow up study showed that family history of C2-C6 venous disease was a significant risk factor for the incidence of C2 varices (p=0.009). After adjusting for age and sex, those with a family history in either first degree relative were 1.7 (95% CI 1.1-2.7) times more likely to develop C2 varices than those with no family history of CVD. The association was significant for maternal (p=0.04) but not for paternal family history (p=0.20). There is no known anatomical or genetic reason why maternal family history would increase the risk of developing varicose veins but paternal history would not. One explanation for the lack of association on the paternal side is that participants may have been more aware of varicose veins in their mother than in their father. In this study, paternal family history was reported approximately half as frequently as maternal family history. Yet there was no significant difference in the prevalence of C2 varices in men and women. This suggests that the lack of a statistical association is not a true finding but rather a consequence of underreporting in this study.

The only other study to examine the effect of family history on the incidence of CVD was the Tampere Study, where the odds ratio of developing varicose veins was 1.6 (95% CI 1.1-2.3). However, only 2.4% of the study sample was examined for C2 varices. Several cross-sectional studies have estimated the effect of family history on the prevalence of CVD but the magnitude of risk has varied widely (Carpentier 2004, Criqui 2003). It has been postulated that genetics may have a role in the pathogenesis of C2 varices and C3-C6 CVI (Krysa 2012). However, positive family history does not automatically mean a genetic cause. The family often share the same environment and other lifestyle factors so are therefore at a similar risk of CVD.

The design of this follow up study provided a unique opportunity to measure the effect of family history on CVD. Only those who did not have C2 varicose veins at baseline were included in the incidence study. Family history was elicited at baseline and therefore it was unaffected by the participant's own varicose vein status during follow up. Therefore the potential for recall bias was minimized. However, it is important to acknowledge that family history was determined based on information obtained from study participants themselves, without consulting or examining relatives. It is possible that patients with varicose veins were more likely to be aware of any relatives who also suffer from the condition. Ideally, the evaluation of family history in the aetiology of CVD would involve studying a number of families of several generations, with family members examined at the same age. However, such a methodology was not feasible in the present study.

12.9.3 Medical history

This follow up study measured the association between medical conditions including DVT, pulmonary embolism, phlebitis, hernia, haemorrhoids, swollen and fractured leg and the development of CVD and venous reflux. However, none of these conditions were associated with the incidence of C2 varicose veins at follow up (all $p>0.05$). Inguinal hernia was the only medical condition identified as a significant risk factor in the development of C3-C6 CVI ($p=0.01$). After adjusting for age and sex, participants with a history of hernia at baseline were over three times more likely to have C3-C6 CVI at follow up (OR 3.1, 95% CI 5.9-10.9).

Deep vein thrombosis is an established contributing factor to the development of varicose veins. The thrombus can either damage the valves directly thus causing reflux or it can impede the vein wall and cause it to dilate and become varicose (Ibrahim 1996). Phlebitis, or inflammation of the vein, often occurs after a DVT and is also associated with CVD (Meissner 2002). It is interesting to note that in this study, both conditions were associated with an increased incidence of C2 varices (both $p<0.05$). However, after adjusting for age and sex, the associations were no longer significant. This could be explained by the small number of participants with a history of these conditions. A larger subgroup with a history of DVT or phlebitis is required to estimate the true association with the incidence of varicose veins. There has been little research linking inguinal hernia with CVI, yet it was a significant risk factor in this study. Again, there were very few participants with a hernia at baseline and therefore the sample is too small to draw any meaningful conclusions.

12.9.4 Pregnancy

Results of this follow up indicated a trend where the incidence of C2 varices increased linearly with number of pregnancies. Although not statistically significant ($p=0.14$) this could have been due to the small numbers in this study. Only 62 of 332 women developed C2 varices during follow up. Therefore the proportion of incident cases on whom to test the effect of parity was very small. The Tampere Study was considerably larger than the Edinburgh Vein Study (n=2,854 women). The estimated risk of developing varicose veins was 2-fold in women with 3 or more pregnancies compared to nulliparous women. However, as previously discussed, a major limitation of the Tampere Study was that venous status was based on self-diagnosis. Nevertheless, despite this limitation, evidence from both the Edinburgh Vein Study and Tampere Study suggests that the incidence of varicose veins is higher in multiparous women.

Prevalence studies suggest that parity is a risk factor for varicose veins (Abramson 1981, Kakande 1981, Komsuoglu 1994, Novo 1988, Stvrtinova 1991, Widmer 1978). The Basle Study demonstrated a significantly higher age-adjusted prevalence of trunk varices in parous women compared with nulliparous women (Widmer 1978). Evidence also points towards a positive relationship between prevalence and an increasing number of pregnancies (Beaglehole 1975, Hirai 1990, Laurikka 1993, Maffei 1986, Novo 1988, Sadick 1992, Sisto 1995). In the Tampere study, the prevalence of varicose veins in women with 0, 1, 2, 3 and 4 or more pregnancies were 32%, 38%, 43%, 48% and 59% respectively (Laurikka 2002).

There are several physiological changes during pregnancy which could contribute to the development of varicose veins. Hormone levels, in particular oestrogen and progesterone, increase dramatically and evidence has shown that the varicose part of the saphenous vein contains more oestrogen and progesterone receptors (Masiah 1999). Secondly, blood flow and volume increase, which can lead to subsequent vein dilatation (Cordts 1996, Sparey 1999). Results on the reversibility of pregnancy-induced dilated veins are conflicting. One study found that although the diameter of competent and incompetent GSV and SSV increased during pregnancy, they decreased during the postpartum period to return to their baseline values (Boivin 2000). A more recent study found that vein dilation is not fully resolved after delivery, suggesting that during pregnancy structural changes in the vein walls may be permanent and even deteriorate in subsequent pregnancies (Pemble 2007). This could explain the increased risk of developing varicose veins with the threshold of 3 pregnancies.

12.9.5 Oral contraceptive use

In this study, oral contraceptive use was not significantly associated with an increased incidence of CVD (P>0.05). These results concur with the Tampere Study, which is the only other study to date to measure the effect of oral contraceptive use on the incidence of C2 varices (Laurikka 2002). Interestingly, in both the Edinburgh Vein Study and Tampere Study, the incidence of C2 varicose veins was lower in women who had previously used oral contraceptives. Although age was a confounding factor in both studies, the lower incidence observed could also be explained by the fact that general practitioners may be less likely to prescribe oral contraceptives to women with C2 varicosities due to the proven thrombotic risk associated with the contraceptive pill and the belief that this risk is increased in those with varicose veins. This theory is supported by results from the EVS follow up, where, after adjusting for age, oral contraceptive use was twice as high in female participants free from varicosities than those with C2 varicose veins. Widmer et al reported no difference in the prevalence of trunk varices in women aged 25-44 years when comparing oral contraceptive users (current or ex) with those who had never used contraceptives (Widmer 1978). It must be noted that the Basle study was conducted in 1978, at which time the oral contraceptive had been prescribed in Switzerland for only the previous four years.

12.9.6 Hormone replacement therapy

Follow up data suggested that the incidence of C2 varicose veins was higher in women who had been on HRT. However this association diminished after adjusting for age as a confounding factor. The Tampere Study also found that after accounting for age, HRT use did not increase the risk of developing varicose veins or CVI. Few studies have examined the relationship between hormonal medication and the prevalence of CVD.

12.9.7 Mobility at work

Mobility at work was not a significant risk factor for the incidence of C2 varicosities, C3-C6 CVI nor venous reflux ≥ 0.5 seconds duration in this study. Evidence on the effect of mobility at work on prevalence of CVD is conflicting. Some studies reported that participants who stood for prolonged periods of time were at increased risk of varicose veins (Abramson 1981, Brand 1988, Kakande 1981, Lee 2003, Pinto 1995, Sadick 1992, Sisto 1995) while other studies found no evidence (Maffei 1986, Scott 1995, Stvrtinova 1991). Results should be interpreted with caution given the difficulty in ascertaining participants' work place posture, particularly over many year of work. Although standing may be an aggravating factor for varicose veins, it is unlikely to be a primary cause. There is no evidence that Africans, for example, stand for less time than Europeans, yet the prevalence of CVD in the former is considerably less than in the latter.

12.9.8 Smoking

Smoking was not a risk factor for developing C2 varicose veins, C3-C6 CVI or venous reflux in this study. The Tampere Study showed that smoking did not increase the incidence of varicose veins (OR 1.3, 95% CI 0.9-1.8). However, a significant association was found in those who reported smoking at least 15 cigarettes per day (OR 1.8, 95% CI 1.1-2.8). As mentioned previously, the results of this study should be interpreted with caution because the accuracy of the diagnosis of varicose veins is questionable given that venous disease was based on self-diagnosis.

Smoking is one of the most common risk factors measured in prevalence studies but none have found any significant association (Brand 1988, Kröeger 2004, Lee 2003, Scott 1995, Sisto 1995). A case control study in France reported a dose-effect relation of tobacco smoking on CVI, with an adjusted odds ratio of 1.4 (95% CI 0.9-2.2) for 10-19 cigarettes per day to 2.1 (95% CI 1.4-3.2) for ≥ 20 cigarettes per day in men and from 1.8 (95% CI 1.3-2.3) to 2.4 (95% CI 1.7-3.4) in women, respectively compared to non-smokers (Gourgou 2002). There are obvious issues in measuring smoking habits. Recall bias, particularly when measuring cigarette packets smoked over a lifetime, is common. Furthermore, legislation prohibiting smoking in public places has led to the widespread belief that it is a socially unacceptable behaviour. Therefore there is a tendency for study participants to under-report smoking in research studies.

12.10 PUBLIC HEALTH IMPLICATIONS OF THE EDINBURGH VEIN STUDY

The Edinburgh Vein Follow Up Study has estimated that approximately 1.4% of the general population will develop C2 varicose veins every year. In Edinburgh, which has a population of approximately half a million people, this equates to 7,000 new cases of varicose veins a year. While the majority of new C2 varices are mild, over time they may progress to more severe conditions of CVI. Venous ulceration is a chronic condition which places major demands on nursing service and incurs a large cost to the NHS. The question must be asked if it is worth operating on varicose veins to prevent more severe complications. There are four important issues to consider when making this assessment: health service utilisation and provision, and the effectiveness and cost-effectiveness of treatment.

12.10.1 Health service utilisation

The Edinburgh Vein Follow Up Study determined that varicose veins affect approximately 40% of the population and that the prevalence increases with age. If this proportion of patients presented for treatment then the demand on the NHS, in terms of primary care appointments and surgical workload, would be huge. However not all patients with varicose veins seek treatment. In the EVS questionnaire administered at follow up, only 20% of participants reported that they had consulted a doctor about their varicose veins. Yet twice this proportion of participants was found to have C2 varices upon examination. The appearance of the leg is one of the most common reasons to seek treatment (Bradbury 1999). Cosmetic motives may account for the higher GP consultation rates for women than for men (Simpson 2004). Furthermore, women are more likely to have had treatment for varicose veins than men (53% and 29% respectively) (Sisto 1995).

12.10.2 Health service provision

The prevalence of C2 varicose veins has logistic implications for the provision of services for assessment and treatment. Assessment and diagnosis of C2 varices or C3-C6 CVI is made based on the signs observed by the GP and the symptoms reported by the patient. However, a patient diagnosed with C2 varicose veins is not necessarily referred for further assessment with a vascular surgeon. NICE published guidelines for appropriate referral from general practice to specialist services for varicose veins, and advised that patients with varicose veins should only be referred if troublesome symptoms were severely impacting quality of life (National Institute for Clinical Excellence 2001). Other factors which influence referral for further assessment include patient preference, risk of complications, policies of local health care providers and waiting lists for treatment (Simpson 2004).

Varicose veins incur long waiting lists for assessment and treatment. A survey of members of the Vascular Surgical Society of Great Britain and Ireland, reported that the median waiting time to be seen in a vascular clinic was 12 weeks (Lees 1999). The mean waiting time for surgery in NHS England (2002-3) was approximately 216 days, (Michaels 2006). Waiting lists remain long despite the rapid growth of varicose vein day surgery in recent years and the subsequent decrease in length of stay for these patients (Simpson 2004). Varicose veins are generally perceived as low priority. A study which rated waiting lists by expected level of benefit to the patient ranked varicose vein surgery lowly when considering benefits against health service resources (Gudex 1999).

Private health care is an option for patients who can afford it. For patients seeking treatment for cosmetic reasons, this may be the only option due to NHS restrictions on surgery for cosmetic complaints. Many private hospitals offer non-surgical removal of varicose veins. Approved by NICE, laser treatment is an attractive treatment option as it requires only a local anaesthetic, can be performed as a day case without hospital admission and evidence has shown that it has a faster recovery time than conventional surgery (Eberhardt 2005)

The number of varicose veins operations performed in Scotland has decreased. According to the Information Services Division (ISD), 4,435 varicose vein operations were performed throughout hospitals in Scotland in 2006/2007. By 2010/2011 the figure was 3,574, equivalent to a decrease of 19.4% over 4 years. Several factors could account for this decrease. Firstly, as the NICE guidelines only recommend referring those with severe varicose veins, NHS health boards now request a higher threshold of clinical severity before surgery is considered. Secondly, varicose vein operations are rarely urgent and may therefore tend to be cancelled due to lack of time or scarce resources. Thirdly the introduction of laser treatment particularly in private health care may result in fewer patients seeking NHS treatment. It is vital that health authorities determine the adequate level of treatment which should be provided in order to give patients maximum benefit.

12.10.3 Effectiveness of treatment

Treatment of varicose veins is intended to prevent complications such as CVI and venous ulceration and to relieve symptoms. However, there is no national consensus as to which varicose veins should be treated based on site of incompetence or severity. Additionally there is no strict guideline as to which treatment should be offered. Many studies have examined the effectiveness of different treatment for varicose veins and it is out with the scope of this thesis to examine this. A key question in measuring the effectiveness of treatments is can they prevent progression to venous ulceration. Long-term epidemiological and clinical studies are required to demonstrate the benefits of surgery over new treatments such as laser therapy and radiofrequency ablation.

12.10.4 Cost-effectiveness

The cost effectiveness of varicose treatment was assessed within a randomised clinical trial (REACTIV trial). Economic analysis determined that standard surgical treatment of varicose veins by ligation and stripping is a cost effective treatment for varicose veins, with an ICER well below the threshold normally considered appropriate for funding of treatments within the NHS.

12.11 THE FUTURE

Varicose veins are an important problem and in an ageing population, the incidence and prevalence is likely to rise. It is important to identify patients at risk of progressing so that proven effective and cost-effectives treatment can be applied to halt deterioration to more serious disease. The Edinburgh Vein Follow Up Study has also examined the progression of CVD. Results could aid the design of a clinical decision tool which may assist clinicians in deciding who should be offered treatment.

CHAPTER 13: CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

13.1 CONCLUSIONS

Chronic venous disease (CVD) is a term covering the spectrum of disease ranging from C2 varicose veins to C3-C6 chronic venous insufficiency (CVI). The Edinburgh Study was a population based cohort in which the baseline sample underwent a 13 year follow up examination to measure the prevalence and incidence of CVD, venous reflux and risk factors associated with these conditions. The following conclusions can be drawn from the study:

13.1.1 Prevalence of chronic venous disease

- The prevalence of C2 varicose veins increased from baseline to follow up.
    - The number of cases of mild C2 varicose veins decreased from 30.8% (95% CI 27.8-33.9) at baseline to 21.8% (95% CI 19.2-24.7) at follow up ($p<0.001$), possibly due to observer error.
    - The number of moderate cases of C2 varices increased from 5.8% (95% CI 4.4-7.5) at baseline to 11.1% (95% CI 9.2-13.4) at follow up, while the number of severe C2 varices increased from 0.3% (95% CI 0.1-1.0) at baseline to 6.3% (95% CI 4.8-8.1) at follow up (both $p<0.001$), suggesting deterioration in C2 varices during the 13-year follow up.

- The prevalence of C2 varicose veins increased with age from 14.3% (95% CI 4.0-40.0) in those aged 25-34 years to 50.6 (95% CI 45.3-55.9) in those aged over 65 years (p<0.001).
- The prevalence of C2 varicose veins was similar in men (40.0%, 95% CI 35.3-44.5) and women (38.6%, 95% CI 34.4-42.9) (p=0.67).
- C2 varicose veins affected the right (29.6%, 95% CI 26.7-32.8) and left (28.7%, 95% CI 25.9-31.8) legs in equal proportions (p=0.57).
- C2 varicose veins were not associated with social class (p=0.79).
- C1 telangiectases were significantly more common in women (90.2%, 95% CI 87.3-92.5) than in men (79.0%, 95% CI 74.7-82.7) (p<0.001).
    - Mild C1 telangiectases were more common in men (65.9%, 95% CI 91.1-70.4) than in women (62.2%, 95% CI 57.9-66.4) (p=0.001).
    - Moderate C1 telangiectases were more common in women (23.3%, 95% CI 19.7-27.2) than in men (11.0%, 95% CI 8.3-14.5) (p<0.001). Severe C1 telangiectases were also more prevalent in women (4.7%, 95% CI 3.2-6.9) than in men (2.1%, 1.0-4.0) (p<0.001).
- The prevalence of C3-C6 CVI increased from baseline to follow up (p<0.001)
    - The most common form of CVI was C3 corona phlebectatica (16.7%, 95% CI 14.4-19.3).
- The prevalence of C3-C6 CVI increased with age, from 7.1% (95% CI 1.3-31.5) in those aged 25-34 years to 32.6% (95% CI 27.9-37.8) in those aged over 65 years (p<0.001).
- The prevalence of C3-C6 CVI did not differ by gender (p=0.18) nor social class (p=0.79).
- Clinical signs of C3-C6 CVI affected the left leg (17.6%, 95% CI 15.2-20.3) more often than the right leg (16.7%, 95% CI 14.4-19.3) (p<0.001).

13.1.2 Incidence of C2 varicose veins and C3-C6 chronic venous insufficiency

- The 13 year incidence of C2 varicose veins was 18.2% (95% CI 15.2-21.6).
    - Approximately 1.4% (95% CI 1.1-1.7) of the study sample developed new C2 varicose veins each year.
    - The majority (87%) of new C2 varices were classified as mild.
- The incidence of C2 varices increased with age in women ($p<0.001$) but not in men ($p=0.23$)
- The incidence of C2 varicose veins was similar in men (10.7%, 95% CI 7.2-15.5) and women (8.1%, 95% CI 5.7-11.6) ($p=0.32$).
- The incidence of C2 varicose veins was similar in the right (11.9%, 95% CI 9.5-14.9) and left leg (11.7%, 95% CI 9.3-14.7) ($p=0.52$).
- Social class had no significant effect in the development of C2 varices ($p=0.95$).
- The 13 year incidence of C3-C6 CVI was 9.2% (95% CI 7.0-11.9).
    - Annual incidence rate of 0.7% (95% CI 0.5-0.9).
    - Majority of new cases of CVI were C3 corona phlebectatica (5.3%, 95% CI 3.7-7.5).
    - Only 0.5% (95% CI 0.2-1.6) of study participants developed a C5 or C6 venous ulcer during the 13 year follow up.
- The incidence of C3-C6 CVI increased with age in men and women ($p<0.001$)
- There were no gender differences in the incidence of C3-C6 CVI ($p=0.32$).

13.1.3 Prevalence and incidence of venous reflux ≥ 0.5 seconds duration

- The prevalence of venous reflux ≥ 0.5 seconds duration at follow up was 23.8% (95% CI 20.7-27.3), 6.5% (95% CI 4.9-8.3) and 11.0% (95% CI 9.0-13.5) in the superficial, deep and combined systems.
    - Reflux was most common in the great saphenous vein (21.6%, 95% CI 18.7-24.9).
    - Superficial reflux was more common in women (28.15, 95% CI 23.6-33.3) than in men (18.4%, 95% CI 14.4-23.1) ($p<0.001$).
    - The prevalence of superficial reflux increased with age ($p<0.001$).
- The incidence of venous reflux was 2.6% (95% CI 1.2-4.9), 8.8% (95% CI 5.9-12.7) and 1.3% (95% CI 0.4-3.2) in the deep, superficial and combined venous systems respectively.
    - Age was not associated with the incidence of reflux ($p>0.05$).
    - New cases of venous reflux affected men (10.7, 95% CI 6.1-17.5) and women (14.2%, 95% CI 9.5-20.8) equally ($p=0.45$).

13.1.4 Prevalence of venous reflux and incidence of C2-C6 CVD

- The risk of developing C2 varicose veins was lowest in those with no reflux and increased linearly in those with deep (OR 1.1, 95% CI 0.5-2.4), superficial (OR 2.6, 95% CI 1.2-6.0) and combined (OR 4.0, 95% CI 1.3-17.3) reflux respectively.
- Venous reflux was not associated with the incidence of C3-C6 CVI (OR 1.9, 95% CI 0.6-6.1) but small numbers may be obscuring a trend.

13.2.4 Risk factors for the incidence of C2-C6 CVD

- There was no association between BMI and C2 varicose veins (p=0.43) but obese patients were over 4 times more likely to develop C3-C6 CVI (OR 4.5, 95% CI 3.3-6.9).
- Pregnancy appeared to increase the risk of developing C2 varicose veins (p=0.14) but was not associated with C3-C6 CVI (p=0.42).
- Family history of venous disease increased the likelihood of developing C2 varices (OR 1.7, 95% CI 1.1-2.7) but was not a risk factor for C3-C6 CVI (OR 1.3, 95% CI 0.7-2.5).

13.3 RECOMMENDATIONS FOR FUTURE RESEARCH

- Further research, based on a larger sample size, is required to clarify the risk factors for incidence of C2 varicose veins and C3-C6 CVI. This could be achieved by combining all population studies on venous disease in a meta-analysis. The quality of each study and the sample size would be taken into account and weighted accordingly. The overall estimate of effect would identify the most important risk factors associated with the development of C2 varices and C3-C6 CVI, and may inform measures to permit disease progression

- The role of venous reflux ≥ 0.5 seconds duration in the development of C2 varicose veins and C3-C6 CVI remains unclear due to the small numbers in this study. Further large scale cohort studies where the sample is followed up over a long period of time are required to clarify the association between venous reflux and the aetiology of C2 varices and C3-C6 CVI.

- Further studies are required to determine the extent to which venous reflux ≥ 0.5 seconds duration is a predictor of C2 varicose vein and C3-C6 CVI progression. The Edinburgh Vein Follow Up Study has examined this relationship. Results will be used to design a clinical scoring tool to help clinicians in deciding who would benefit most from treatment to slow or halt disease progression.

- Further work is required on the correlation between symptoms, quality of life and venous disease. The questionnaire at both the baseline and follow up stages of the study enquired about symptoms of venous disease, while quality of life was measured in follow up participants only. Analysis of this data is already planned for this study population and will help to measure the quality of life in patients with chronic venous disease and identify those whose symptoms may be relieved by treatment.

- Family and genetic studies are required to determine the extent to which venous disease is an inherited or an acquired condition. Blood samples from all baseline EVS participants are stored and awaiting genetic analysis.

- Future studies are required in order to clarify the cut-off point at which duration of reflux becomes clinically significant in different specific vein segments. This will help the interpretation of results not only in clinical situations but also in the presentation of research findings.

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APPENDIX 1: JOURNAL OF VASCULAR SURGERY PUBLICATION

Journal of Vascular Surgery
Venous and Lymphatic Disorders

Incidence of chronic venous disease in the Edinburgh Vein Study

Lindsay Robertson, MSc,[a] Amanda J. Lee, PhD,[b] Christine J. Evans, MB, ChB,[c] Sheila Boghossian, MSc,[a] Paul L. Allan, FRCR,[a] C. Vaughan Ruckley, ChM, FRCSE,[a] and FGR Fowkes, FRCPE,[a] *Edinburgh and Aberdeen, United Kingdom*

Background: Epidemiologic research in chronic venous disease has focused on prevalence and associated risk factors. Evidence on the risks and incidence that this condition will develop is limited. The aim of this study was to measure the incidence of new varicose veins and chronic venous insufficiency (CVI) in an adult population and to investigate risk factors associated with the development of these conditions.

Methods: The Edinburgh Vein Study is a cohort study of a random sample of the general population. Invitations were sent to 1456 men and women at baseline to participate in a 13-year follow-up examination. Each participant completed a questionnaire on lifestyle and medical history and underwent an examination that included clinical classification of venous disease.

Results: After a mean follow-up of 13.4 (standard deviation, 0.4) years, 880 of 1456 individuals participated (60.4% response). The overall incidence (95% confidence interval [CI]) of C_2 varicose veins was 18.2% (15.2%-21.6%), giving an annual incidence rate of 1.4% (1.1%-1.7%), with incidence rates similar in men and women: the 13-year age-adjusted incidence of varicose veins was 15.2% (10.4%-20.0%) in men and 17.4% (13.1%-21.7%) in women ($P = .97$). The 13-year incidence of varicose veins increased consistently with age from 9.8% in those aged 18 to 34 years to 25.7% in those aged 55 to 64 years ($P < .001$). The 13-year incidence (95% CI) of CVI was 9.2% (7.0%-11.9%), and the annual incidence rate was 0.7% (0.5%-0.9%). The incidence of CVI was similar in men and women and increased consistently with age ($P < .001$). Participants with a family history of venous disease were more likely to develop C_2 varicose veins (odds ratio, 1.75; 95% CI, 1.12-2.71). Obesity was associated with the development of CVI: the 13-year incidence (95% CI) was 6.1% (3.7%-9.6%) in those who were of normal weight and 23.6% (14.2%-37.0%) in obese participants, with an age-adjusted odds ratio of 3.58 (1.70-7.56).

Conclusions: The Edinburgh Vein Study is one of a few cohort studies to report the incidence of varicose veins and CVI in the general population. The incidence of varicose veins and CVI did not differ significantly by sex and was strongly associated with increasing age. The risk of developing varicose veins was increased in those with a family history, and the risk of CVI was increased in those with higher body mass index. (J Vasc Surg: Venous and Lym Dis 2013;1:59-67.)

Chronic venous disease ranges from asymptomatic venous valve incompetence to varicose veins, skin changes, and venous ulceration. Such changes are termed chronic venous insufficiency (CVI). CVI causes considerable morbidity and has high treatment costs. The economic cost of treating venous leg ulcers in the United Kingdom was estimated to be £300 to £400 million per year.[1]

Most epidemiologic research has focused on the prevalence of varicose veins and ulceration.[2-11] Prevalence is useful in estimating the total burden of disease in a population but does not provide evidence on the risk of acquiring new varicose veins and CVI. Few studies[5,12-15] have measured the incidence of varicose veins and CVI and are prone to methodologic issues, including relying on participants self-reporting venous disease or lack of a standardized diagnosis. Thus, evidence regarding the incidence of chronic venous disease is inconclusive. Good-quality cohort studies with an adequate follow-up are needed to calculate the true incidence of varicose veins and CVI. The Edinburgh Vein Study is a prospective cohort study that measured the incidence of new varicose veins, CVI, and associated risk factors in an adult population.

METHODS

This study was approved by Lothian Research Ethics Committee, and each participant gave informed written consent.

Study design. The Edinburgh Vein Study is a prospective population-based cohort in which a random sample of 1566 individuals, aged 18 to 64 years, were selected from general practices in Edinburgh, Scotland, and examined between 1994 and 1996. The methods used in the Edinburgh Vein Study baseline survey have been published previously[16,17] and

From the Centre for Population Health Sciences, University of Edinburgh, Edinburgh[a]; the Department of General Practice and Primary Care, University of Aberdeen, Aberdeen[b]; and NHS Lothian, Edinburgh.[c]

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Reprint requests: Lindsay Robertson, University of Edinburgh, Centre for Population Health Sciences, Teviot Pl, Edinburgh EH8 9 AG, UK (e-mail: lindsay.robertson@ed.ac.uk).

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included categorization of venous disease using the Basle classification and a duplex scan to measure venous reflux. The follow-up examination was conducted 13 years later.

Details of 1566 baseline participants were linked to the Lothian Community Health Index to provide updated addresses and identify the general practice where each participant was registered. All surviving baseline participants were sent an invitation pack. On receiving an affirmative reply, a follow-up appointment was arranged.

Clinical examination. At follow-up, all participants underwent a clinical examination at the Wellcome Trust Clinical Research Facility at the Western General Hospital, Edinburgh. Height was measured to the nearest 5 mm without shoes using a stadiometer. Weight, without shoes or outdoor clothes, was measured to the nearest 100 g on a digital Soehnle scale (Nassau, Germany). Venous reflux was also assessed, the results of which will be presented in a subsequent report. A standardized questionnaire gathered information on demographics, family history, and previous treatment of venous disease, medical history, smoking status, physical exercise, and mobility at work. Obstetrical history was documented for all women.

At follow-up, assessment of venous disease was made according to the CEAP classification.[18] CEAP was not available at the baseline assessment, so venous disease was determined according to the Basle classification, which is based on clinical observation of venous disease and subdivides telangiectasis, reticular veins, and varicose veins into grades of severity 1 to 3 determined according to the degree and extent of the tortuosity and prominence of the veins.[19] To ensure direct comparison between results at baseline and follow-up, and to permit comparison with other studies that have used the CEAP classification, CEAP and Basle classifications were both used at follow-up. For C_1 and C_2 veins, each class was subdivided into severity 1 to 3 according to Basle. CVI was graded according to the CEAP classification only as it corresponds directly with Basle: Basle grade 1 corresponds to CEAP C_3, grade 2 to C_4 and grade 3 to C_5 to C_6.

To classify venous disease, participants stood on a platform with their feet in three standard positions: (1) facing toward the examiner with heels together and forefeet apart, (2) facing away from the examiner in a similar position, and (3) facing away from the examiner with feet parallel. All participants stood for a minimum of 2 minutes before classification to allow blood to pool in their legs. The limb assigned the higher C value or Basle grade (ie, worse disease) was used for each participant throughout the analysis.

The participants' legs were also photographed on the platform in the three positions, with the camera positioned to allow visualization of the leg from the foot to the groin. Two study investigators analyzed the digital photographs and independently graded venous disease according to the classification systems as outlined. If the classification of the two observers viewing the photographs differed, discussion was held until a consensus classification for each participant was achieved.

Statistical analysis. Information from recording forms was checked and double-entered by two investigators into the university computer system. Statistical analysis was performed with SPSS-X software (SPSS Inc, Chicago, Ill). A value of $P \leq .05$ was used to denote statistical significance. The χ^2 test was used to assess the association of incidence with sex and to assess the linear trend for age group. Intra-rater and inter-rater percentage agreements of the venous classification and of the clinical and photographic results were calculated and compared using the κ statistic.

Quality control. Three quality control exercises were used during the study to minimize variations in measurements by the four observers and to improve the accuracy of the results:

First, 49 random participants underwent a second examination to compare interobserver variations. The four observers were grouped into pairs for comparisons to be made. The same leg was scanned independently for each participant by two observers and both legs were classified. Results of the interobserver reliability indicated agreement ranging from 77% to 100% for each class of clinical disease, and κ scores ranged from 0.78 to 1.00. For the assessment of intraobserver variability, each participant underwent a second clinical examination by the same observer who conducted the first examination, with a minimum of 12 weeks between. Results showed the level of agreement for each observer was 74% to 100% and all $\kappa > 0.6$.

Second, an examination classification was compared with the photographic classification, and measures of agreement were obtained for individual participants. Results showed that spider and reticular veins, and also corona, were classified at a higher grade from photographic evidence, whereas varicose veins were classified at a higher grade on examination. Although the preference was to use examination rather than photographic data, results of the variability checks indicated that the following amendments would improve the accuracy of the data to be included in the statistical analysis:

- Classification of spider and reticular veins was based on photographic evidence, where available, because it was based on two observers who had independently classified venous disease.
- Classification of CVI was based predominantly on the examination with adjustments for photographic findings for corona. This was because corona was seen more frequently in photographs than at examination, and because the photographs were independently classified by two observers, data from the photographs were considered more accurate.

Third, the frequencies of clinical classifications by the four observers were compared to check for differences. Analysis showed that one observer reported fewer grade 1 varicose veins on examination. However, when this observer's classification based on photographic evidence was compared with the other three observers, no significant difference in the prevalence of grade 1 varicose veins was

found, suggesting an under-reporting at examination. As a result, participants graded 0 by this observer at the clinical examination were corrected to a grade 1 if that was the finding on the photographic evidence. Another observer at examination reported a higher prevalence of eczema than the other three observers, suggesting possible over-reporting. Again, an amendment was made so that the classification of eczema for that observer was based on photographic evidence.

RESULTS

Recruitment of the 1566 baseline participants is shown in Fig 1. Of 1456 subjects eligible for the follow-up study, 880 were examined, giving a response rate of 60.4%. To measure the representativeness of the final study sample to the baseline study population, data from the baseline

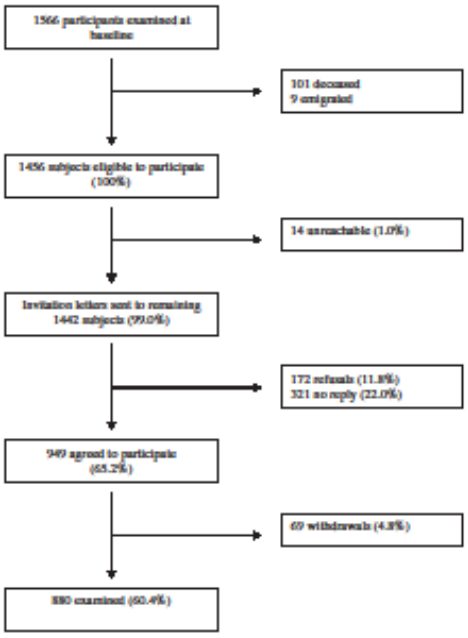

Fig 1. Flow chart shows the recruitment process in the follow-up phase of the Edinburgh Vein Study, starting with 1566 participants who took part in the baseline phase of the study. Of the 1465 surviving baseline participants, 880 agreed to participate and underwent a follow-up examination, resulting in a 60.4% response rate. The proportion of baseline study participants who did not take part in the study are listed according to various reasons: *no reply*, did not reply despite two invitation letters and three attempts to contact them by telephone; *refusals*, replied but refused to take part in the follow-up study; *unreachable*, moved to another health authority and the address could not be traced; *withdrawals*, initially agreed to participate but subsequently withdrew or failed to attend.

phase were compared between participants and nonparticipants in the follow-up study. No significant differences were found between the baseline prevalence of varicose veins or CVI in participants and nonparticipants in the follow-up study. Reflux, symptoms, and family history of venous disease were also similarly distributed.

At follow-up, 99.5% of the participants were white and 55.7% were women. The mean (standard deviation) age of all participants was 60.0 (11.5) years, and by sex was 60.4 (11.3) years for men compared with 59.7 (11.6) years in women ($P = .32$).

At baseline, 555 participants (63.1%) of the 880 examined at follow-up were free of C_2 varicose veins. At follow-up, C_2 varicose veins had developed in 101 of these participants, an overall incidence of 18.2% (95% confidence interval [CI], 15.2%-21.6%). The mean (SD) follow-up period of the study was 13.4 (0.4) years, so that the average annual incidence rate was 1.4% (95% CI, 1.1%-1.7%). Of 101 new cases of varicose veins, 36 were in the right leg only, 35 in the left leg only, and 30 in both legs. According to the Basle classification, 87% of affected participants had mild grade 1 varicose veins. The 13-year incidence (95% CI) of grade 1 (mild), 2 (moderate), and 3 (severe) varicose veins was 15.7% (12.9%-18.9%), 2.3% (1.4%-4.0%), and 0.2% (0.1%-1.0%), respectively.

Of 880 participants examined at follow-up, 546 (62.0%) had no CVI at baseline, of whom 50 developed C_3 to C_6 CVI at follow-up, an incidence (95% CI) of 9.2% (7.0%-11.9%) and an annual incidence rate of 0.7% (0.5%-0.9%). The most common form of CVI was C_3 (corona phlebectatica and venous edema). Only three (0.5%) participants developed venous ulceration (C_5-C_6). The 13-year incidence (95% CI) of grades C_3, C_4, and C_5 to C_6 CVI was 5.3% (3.7%-7.5%), 3.3% (2.1%-5.2%), and 0.5% (0.2%-1.6%), respectively.

The 13-year incidence of varicose veins and CVI by sex is reported in Table I. The overall incidence of C_2 varicose veins was not significantly different between women (18.6%, 95% CI, 14.8%-23.1%) and men (17.7%, 95% CI, 13.2%-23.2%; $P = .97$). When examined by severity, no significant difference in incidence of varicose veins between sexes was found. The incidence of CVI was 10.6% (95% CI, 7.2%-15.5%) in men and 8.1% (95% CI, 5.7%-11.6%) in women ($P = .25$). Sex differences were not statistically significant when CVI class was analyzed individually.

Fig 2 displays the incidence of C_2 varicose veins by age in men and women. For all participants, the incidence of varicose veins increased linearly with age, from 9.8% (95% CI, 5.9%-15.8%) in those aged 18 to 34 years at baseline to 25.7% (95% CI, 18.5%-34.4%) in those aged 55 to 64 years ($P < .001$ for trend). When analyzed by sex, the incidence of varicose veins appeared to increase with age more consistently in women than in men. The incidence in women increased with every baseline age group ($P < .001$), so that the rate was three times higher at age 55 to 64 years than at age 18 to 34 years. In men, however, the rate increased with age but was lower in those aged

Table I. The 13-year incidence of varicose veins and chronic venous insufficiency (*CVI*) in men and women

		Incidence in						
		Men		*Women*		*Men and women*		
CEAP classification	*Basic grade*	*No.*	*% (95% CI)*	*No.*	*% (95% CI)*	*No.*	*% (95% CI)*	P[a]
Varicose veins[b]								
C_2	1	33	14.9 (10.8-20.2)	54	16.2 (12.6-20.5)	87	15.7 (12.9-18.9)	.13
C_2	2	5	2.3 (0.9-5.2)	8	2.4 (1.2-4.6)	13	2.3 (1.4-4.0)	.83
C_2	3	1	0.5 (0.9-2.5)			1	0.2 (0.1-1.0)	.26
C_2	Total	39	17.6 (13.2-23.2)	62	18.6 (14.8-23.1)	101	18.2 (15.2-21.6)	.35
CVI[c]								
C_3	1	13	6.0 (3.6-10.1)	16	4.8 (3.0-7.7)	29	5.3 (3.7-7.5)	.65
C_4	2	8	3.7 (1.9-7.2)	10	3.0 (1.7-5.5)	18	3.3 (2.1-5.2)	.78
C_{5-6}	3	2	0.9 (0.3-3.3)	1	0.3 (0.6-1.7)	3	0.6 (0.2-1.6)	.33
C_{3-6}	Total	23	10.7 (7.2-15.5)	27	8.2 (5.7-11.6)	50	9.2 (7.0-11.9)	.25

CI, Confidence interval; *No.*, number in each group with varicose veins/CVI at follow-up.
[a]*P* value based on χ^2 test for differences in varicose veins and CVI by sex.
[b]Incidence of C_2 varicose veins in 555 participants free of C_2 varicose veins at baseline, 221 men, 334 women.
[c]Incidence of CVI in 546 participants free of CVI at baseline, 215 men, 331 women.

55 to 64 years, so that overall the trend was not statistically significant ($P = .23$). The age-adjusted incidence of varicose veins was 15.2% (95% CI, 10.4%-20.0%) in men and 17.4% (95% CI, 13.1%-21.7%) in women.

The incidence of C_3 to C_6 CVI according to age group is presented in Table II. Overall, the incidence of CVI increased with age, from 2.1% in those aged 18 to 34 years to 17.1% in those aged >55 years at baseline ($P < .001$ for trend). When analyzed by sex, the incidence remained significantly associated with age for both men ($P = .003$ for trend) and women ($P = .001$ for trend). The age-adjusted incidence of CVI was 7.5% (95% CI, 4.5%-10.6%) in men and 7.1% (95% CI, 4.4%-9.8%) in women ($P = .25$).

The incidence of C_2 varicose veins by risk factors at baseline is reported in Table III. Participants who were overweight or obese had a slightly greater incidence than those who were of normal weight, but the unadjusted ORs of 1.21 (95% CI, 0.75-1.95) and 1.30 (95% CI, 0.68-2.50) were not statistically significant and were both reduced, adjusting for age and sex. The incidence of varicose veins was slightly higher in women with three or four or more pregnancies but the ORs of 1.25 (95% CI, 0.55-2.85) and 1.88 (95% CI, 0.79-4.45) were not statistically significant. Incidence of varicose veins was associated with previous hormone replacement therapy, but this association was reduced and became nonsignificant after adjusting for age.

Participants with a family history of varicose veins or venous ulceration were more likely to have new varicose veins at follow-up (OR, 1.74; 95% CI, 1.12-2.71). Smoking, oral contraceptive use, and mobility at work were not significantly associated with the incidence of varicose veins.

Table IV reports the incidence of C_3 to C_6 CVI by risk factors at baseline. Participants who were classified as obese

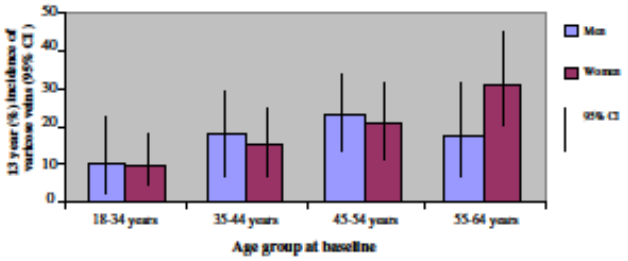

Fig 2. Bar chart shows the 13-year incidence of C_2 varicose veins by age in men and women in the Edinburgh Vein Study follow-up. The *x axis* represents age groups at baseline, and the *y axis* represents the incidence (%) over the 13-year follow-up period. Within the age group, the incidence is split by men and women, as represented by the *two colored bars*. The 95% confidence interval (*CI*) for the incidence is represented by the *vertical line* within each bar, with the *bottom* and *top* of the line representing the lower and upper limit, respectively.

Table II. The 13-year incidence of C_3 to C_6 chronic venous insufficiency (*CVI*) by age in men and women

	Incidence of CVI					
	In men (n = 215)		*In women (n = 331)*		*In men and women (n = 546)*	
Age at baseline (years)	*n/N*	*% (95% CI)*	*n/N*	*% (95% CI)*	*n/N*	*% (95% CI)*
18-34	0/50	0 (0)	3/92	3.3 (1.1-9.2)	3/142	2.1 (0.7-6.0)
35-44	4/55	7.3 (2.9-17.2)	2/77	2.6 (0.7-9.0)	6/132	4.5 (2.1-9.6)
45-54	13/66	19.7 (11.9-30.8)	9/95	9.5 (5.1-17.0)	22/161	13.7 (9.2-19.8)
55-64	6/44	13.6 (6.4-26.7)	13/67	19.4 (11.7-30.4)	19/111	17.1 (11.2-25.2)
P[a]		.001		.003		<.001

CI, Confidence interval; *n/N*, number of total with C_3 to C_6 CVI at follow-up according to CEAP classification.
[a]*P* value from χ^2 linear trend test.

at baseline were more likely to develop CVI at follow-up than those who were of normal weight (OR, 3.58; 95% CI, 1.70-7.56). Parity was associated with a 13-year incidence of CVI ≥9.0% compared with 5.6% in nulliparous women, but the ORs were nonsignificant. Women who had previously used oral contraceptives had a 5.5%

Table III. Incidence of C_2 varicose veins at 13-year follow-up, measured by risk factors at baseline

	Incidence of C_2 varicose veins		*OR (95% CI)*	
Risk factor at baseline	*N/N*[a]	*% (95% CI)*	*Unadjusted*	*Adjusted*[b]
Body mass index[c]				
Normal weight	46/278	16.5 (12.3-21.9)	...	...
Overweight	38/196	19.4 (13.9-26.3)	1.21 (0.75-1.95)	1.03 (0.63-1.70)
Obese	15/73	20.5 (11.9-33.1)	1.30 (0.68-2.50)	1.03 (0.53-2.00)
Pregnancies, No.				
0	15/90	16.7 (9.7-26.9)	...	...
1-2	22/135	16.3 (10.5-24.3)	0.97 (0.42-2.00)	0.63 (0.29-1.37)
3	13/65	20.0 (11.1-33.3)	1.25 (0.55-2.85)	0.72 (0.29-1.75)
≥4	12/44	27.3 (14.8-46.4)	1.88 (0.79-4.45)	1.04 (0.41-2.67)
Oral contraceptive use				
Never	16/72	22.2 (13.2-35.3)	...	...
Ever	45/258	17.4 (12.9-23.1)	0.74 (0.39-1.41)	1.21 (0.59-2.51)
Hormone replacement therapy				
Never	45/273	16.5 (12.2-21.9)		
Ever	17/57	29.8 (18.0-46.8)	2.15 (1.12-4.13)	1.48 (0.73-2.97)
Smoking				
Never smoked	55/292	18.8 (24.3-24.3)	...	...
Former smoker	25/143	17.5 (11.6-25.4)	0.91 (0.54-1.54)	0.86 (0.51-1.46)
Current smoker	21/118	17.8 (11.3-26.7)	0.93 (0.54-1.63)	0.99 (0.56-1.74)
Family history of venous disease				
No	48/324	14.8 (11.0-19.5)	...	...
Yes	51/219	23.3 (17.5-30.4)	1.75 (1.13-2.71)	1.74 (1.12-2.71)
Mobility at work (% of time)				
Sitting				
<50%	57/304	18.8 (14.3-24.1)	...	...
≥50%	44/251	17.5 (12.9-23.3)	0.89 (0.54-1.46)	0.92 (0.56-1.51)
Standing				
<50%	74/405	18.3 (14.4-22.8)	...	...
≥50%	27/150	18.0 (12.1-25.8)	0.93 (0.54-1.58)	0.95 (0.56-1.63)
Walking				
<50%	75/410	18.3 (14.5-22.8)	...	...
≥50%	26/144	18.1 (12.0-26.1)	0.87 (0.49-1.54)	0.84 (0.47-1.49)
Lifting				
<50%	86/486	17.1 (14.2-21.7)	...	...
≥50%	15/69	21.7 (12.6-35.0)	1.38 (0.71-2.71)	1.44 (0.73-2.85)

CI, Confidence interval; *OR*, odds ratio.
[a]*n*, number of participants in each group with C_2 varicose veins at follow-up; *N*, total number of participants within each risk factor group.
[b]Adjusted for age and sex.
[c]Weight category by body mass index (kg/m^2): ***normal weight***, 18.50-24.99; ***overweight***, 25.00-29.99; ***obese***, ≥30. Eight participants, defined as underweight with body mass index <18.50 kg/m^2 were excluded.

Table IV. Incidence of C_3 to C_6 chronic venous insufficiency (*CVI*) at the 13-year follow-up, measured by risk factors at baseline

	Incidence of C_3 to C_6 CVI		*OR (95% CI)*	
Risk factor at baseline	*n/N*	*% (95% CI)*	*Unadjusted*	*Adjusted[a]*
Body mass index[b]				
Normal weight	17/277	6.1 (3.7-9.6)	...	...
Overweight	16/189	8.5 (5.0-13.4)	1.74 (0.89-3.41)	1.22 (0.60-2.47)
Obese	17/72	23.6 (14.2-37.0)	5.00 (2.43-10.32)	3.58 (1.70-7.56)
Pregnancies, No.				
0	5/89	5.6 (2.1-12.4)	...	...
1-2	12/134	9.0 (4.8-15.2)	1.65 (0.56-4.86)	0.89 (0.28-2.79)
3	6/65	9.2 (3.7-19.2)	1.71 (0.50-5.86)	0.77 (0.21-2.85)
≥4	5/43	9.3 (3.0-22.4)	1.72 (0.44-6.77)	0.71 (0.17-3.05)
Oral contraceptive use				
Never	13/72	18.1 (10.0-30.1)	...	...
Ever	14/255	5.5 (3.1-9.0)	0.26 (0.12-0.59)	0.47 (0.19-1.19)
Hormone replacement therapy				
Never	23/271	8.5 (5.5-12.5)	...	...
Ever	4/56	7.1 (2.3-17.2)	0.83 (0.27-2.50)	0.42 (0.13-1.31)
Smoking				
Never smoked	27/290	9.3 (6.3-13.4)	...	...
Former smoker	12/141	8.5 (4.6-14.5)	0.91 (0.44-1.85)	0.82 (0.40-1.70)
Current smoker	11/113	9.7 (5.1-16.9)	1.05 (0.50-2.20)	1.20 (0.56-2.57)
Family history of venous disease				
No	26/319	8.2 (5.4-11.8)	...	...
Yes	23/215	10.7 (6.9-15.8)	1.35 (0.75-2.44)	1.37 (0.75-2.50)
Mobility at work (% of time)				
Sitting				
<50%	31/297	10.4 (7.2-14.6)	...	...
≥50%	19/249	7.6 (4.7-11.7)	0.69 (0.35-1.34)	0.73 (0.37-1.43)
Standing				
<50%	37/401	9.2 (6.6-12.6)	...	...
≥50%	13/145	9.0 (5.0-14.9)	0.80 (0.39-1.63)	0.82 (0.40-1.68)
Walking				
<50%	35/403	8.7 (6.1-11.9)	...	...
≥50%	15/142	10.6 (6.1-17.0)	1.10 (0.53-2.29)	1.06 (0.50-2.24)
Lifting				
<50%	43/479	9.0 (6.6-12.0)	...	...
≥50%	7/67	10.4 (4.6-20.7)	1.09 (0.44-2.71)	1.11 (0.44-2.85)

CI, Confidence interval; *OR*, odds ratio; *n*, number of participants in each group with C_3 to C_6 CVI at follow-up; *N*, total number of participants within each risk factor group.
[a]Adjusted for age and sex.
[b]Weight category by body mass index (kg/m^2): *normal weight*, 18.50-24.99; *overweight*, 25.00-29.99; *obese*, ≥30.

incidence of CVI at follow-up vs 18.1% (OR, 0.26; 95% CI, 0.12-0.59) but this association became nonsignificant after adjusting for age (OR, 0.47; 95% CI, 0.19-1.19). Hormone replacement therapy, family history of venous disease, smoking, and mobility at work were not significantly related to the incidence of CVI.

The incidence of chronic venous disease according to medical history at baseline is reported in Table V. The only medical conditions associated with increased incidence of varicose veins were deep vein thrombosis ($P = .02$) and phlebitis ($P = .03$). No medical condition was found to be significantly associated with the risk of developing CVI.

DISCUSSION

The Edinburgh Vein Study has reported a 13-year incidence of C_2 varicose veins of 18.2% (95% CI, 15.2%-21.6%) and an annual incidence rate of 1.4% (95% CI, 1.1%-1.7%). The 13-year incidence of C_3 to C_6 CVI was 9.2% (95% CI, 7.0%-11.9%), so each year, 0.7% (95% CI, 0.5%-0.9%) of the population developed CVI, alone or accompanied by varicose veins. Most participants who developed varicose veins or CVI were classified as having mild (grade 1) disease at follow-up.

Few other studies have measured the incidence of chronic venous disease. The incidence reported in our study is lower than in the Framingham Study, a longitudinal study with a follow-up every 2 years for 16 years. The annual incidence rate of varicose veins was 2.6% in women and 1.9% in men.[12] In the Bonn Vein Study II, a population-based study in which 1978 of 3072 participants were re-examined after a 6.6-year follow-up, the incidence per year was 2.07% for varicose veins and 1.97% for CVI.[13]

Our study showed that the incidence of chronic venous disease increased by age group. These results are in keeping with the Bochum Study,[15] where the incidence of varicose veins also increased with age, although

Table V. Incidence of C_2 varicose veins and C_3 to C_6 chronic venous insufficiency (*CVI*) at 13-year follow-up in participants free of disease at baseline, measured by medical history at baseline

	Incidence of C_2 varicose veins at follow-up					*Incidence of C_3 to C_6 CVI at follow-up*				
	History of medical condition?					*History of medical condition?*				
	No		*Yes*			*No*		*Yes*		
Variable	*n*	*% (95% CI)*[b]	*n*	*% (95% CI)*[b]	P[a]	*n*	*% (95% CI)*[b]	*n*	*% (95% CI)*[b]	P
Deep vein thrombosis	96	17.6 (14.4-21.5)	5	50.0 (18.3-110.8)	.02	49	9.1 (6.8-12.0)	1	11.1 (0.6-54.8)	.58
Phlebitis	94	17.4 (14.2-21.2)	6	42.9 (917.4-89.1)	.03	46	8.7 (6.4-11.4)	3	23.1 (5.9-62.8)	.10
Pulmonary embolism	10	18.1 (14.8-22.0)	1	50.0 (2.5-246.6)	.33	50	9.2 (6.9-12.1)	0	0	.82
Hemorrhoids	69	18.3 (14.3-23.0)	32	18.1 (12.6-25.2)	.95	32	8.6 (6.0-12.1)	18	10.3 (6.3-15.9)	.54
Hernia	94	17.9 (14.6-21.9)	7	23.3 (10.2-46.2)	.62	42	8.2 (5.9-10.9)	8	26.7 (12.4-50.6)	.10
Swollen leg										
After operation	86	16.9 (13.6-20.8)	8	27.6 (12.8-52.4)	.22	45	8.9 (6.6-11.8)	1	4.0 (0.2-19.7)	.62
After pregnancy[c]	34	20.0 (14.2-27.8)	15	18.1 (10.4-28.8)	.85	13	7.8 (4.3-12.9)	10	12.0 (6.1-21.5)	.39
Other	69	18.1 (14.2-22.7)	14	13.7 (7.8-22.5)	.38	32	8.4 (5.9-11.8)	9	9.1 (4.4-12.7)	>.99
Fractured leg	92	18.4 (14.9-22.4)	9	18.0 (8.8-33.0)	.95	43	8.7 (7.4-13.0)	6	12.2 (5.0-25.5)	.58

CI, Confidence interval; *n*, number of participants with C_2 varicose veins or C_3 to C_6 CVI at follow-up.
[a]Based on χ^2 test for difference between incidence of C_2 varicose veins and C_3 to C_6 CVI by medical condition at baseline.
[b]Incidence of C_2 varicose veins or C_3 to C_6 CVI by history of medical condition at baseline.
[c]Based on 253 women free of varicose veins at baseline.

participants in that study were school children aged 10 to 12 years monitored for 20 years. In the Framingham Study,[12] the incidence of varicose veins did not increase significantly with age. Our study also showed that incidence of CVI was related to age: participants aged 55 to 64 years were almost eight times more likely to develop CVI than those aged 18 to 34 years. The Edinburgh Vein Study is the first to produce convincing evidence that the risk of acquiring chronic venous disease increases with age, a finding that would be expected in a chronic degenerative condition.

We found no significant sex difference in the incidence of varicose veins. The Bonn Vein Study II[13] also found no sex difference. Other evidence indicates a higher incidence in women. The Framingham study reported annual rates of 2.6% in women and 1.9% in men.[12] The Tampere Varicose Vein Study[20] reported rates of 19.2/1000 person-years in women and 8.5/1000 person-years in men. However, that study used a postal questionnaire to obtain information on venous disease data, which might have had biased responses by sex. The Bochum Study[15] found no significant sex differences; however, only 136 participants were monitored for the full duration of the study.

Few studies have measured the incidence of chronic venous disease. Therefore, longitudinal evidence on the contribution of risk factors to the development of this condition is lacking. Obesity, parity, and mobility at work have been postulated as important risk factors but none have shown consistently positive associations in cross-sectional studies with prevalence of chronic venous disease.[9,21,22]

Results from our follow-up study suggest that increased weight is associated with the incidence of chronic venous disease, particularly in the development of CVI, where the risk was 3.6-fold higher in obese participants. A higher proportion of participants who were overweight or obese at baseline developed varicose veins at follow-up, but these results were not statistically significant and might have been confounded by age.

For parity, the Basle study[23] demonstrated a significantly higher age-adjusted prevalence of trunk varices in parous women compared with nulliparous women, and some other studies support these findings.[11,24,25] Indeed, evidence suggests a positive relationship between the prevalence of varicose veins and an increasing number of pregnancies.[8,14,21,26,27] Although our study found no statistically significant association between the number of pregnancies at baseline and the incidence of varicose veins at follow-up, the lack of statistical association must be interpreted with caution due to the small numbers in our study.

Our results suggest that mobility at work was not linked to the development of varicose veins nor CVI. Although the association of standing at work and the incidence of venous disease has not been measured previously, evidence on the association with prevalence is conflicting. Some studies[10,24,26,27] reported that participants who stood for prolonged periods were at increased risk of varicose veins, whereas other studies found no evidence.[11] Results should be interpreted with caution given the difficulty in retrospectively ascertaining subjects' workplace posture, particularly over many years of work.

Family history of venous disease was associated with increased risk of developing varicose veins in our study. Interestingly, family history was not significantly associated with the development of CVI. These results are in keeping with those of Scott et al,[10] where patients with varicose veins were 21.5 times more likely to report a family history than controls ($P = .001$), but family history was not a significant factor in patients with CVI. In studies that rely on questionnaires to gather information on family history, recall bias may be a problem because those with

venous disease may be more aware of disease among family members. However, in a cohort study such as ours, the potential for recall bias was minimized by measuring family history at baseline. Thus, the self-reported evidence from this study indicates a familial susceptibility to development of varicose veins.

The Edinburgh Vein Study has several strengths. The baseline and follow-up studies on representative population samples were conducted in a systematic and rigorous manner. Classification of venous disease was undertaken in a standardized way. The four members of the study team underwent extensive training in venous clinical examination and duplex ultrasound imaging by a team of radiologists and vascular scientists. The four study observers periodically re-examined photographic evidence as a reminder of the two classification systems used.

A limitation of the study was that, despite regular quality control measures during data collection, there was evidence of some inconsistency by observers in the classification of disease on clinical examination. One observer under-reported grade 1 (C_2) varicose veins, whereas another observer over-reported C_4 venous eczema. At both stages of the study, photographs were taken to ensure that supporting evidence was available. Because photographs were not available for all participants, they could not be substituted completely for clinical examination data but were used where feasible to correct for possible misclassification. Although not ideal, we considered this approach to provide the most valid assessment of venous disease, particularly because the appraisal of the photographs was made independently by two observers blind to the results of the clinical examination.

CONCLUSIONS

This follow-up phase of the Edinburgh Vein Study has produced important information on the incidence of chronic venous disease by age and sex in the general population and investigated possible risk factors. We plan to conduct further analyses to determine the effect of venous reflux on the incidence of venous disease.

We thank Angie Balfour and Heather Spence at the Wellcome Trust Clinical Research Facility for data collection and Karen Gallagher and Maggie Glass for training in duplex ultrasound imaging.

AUTHOR CONTRIBUTIONS

Conception and design: FF, AL, CE, CR, PA
Analysis and interpretation: LR, FF, AL, CE, CR, PA
Data collection: LR, SB
Writing the article: LR, FF, AL, CE, CR, PA
Critical revision of the article: LR, FF, AL, CE, CR, PA
Final approval of the article: LR, FF, AL, CE, CR, PA
Statistical analysis: LR, SB, AL
Obtained funding: FF, AL, CE, CR, PA
Overall responsibility: LR

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APPENDIX 2: BASLE CLASSIFICATION OF CHRONIC VENOUS DISEASE

BASLE CLASSIFICATION OF VENOUS DISEASE

AUTHOR	CLASS	DEFINITION
Widmer 1978	1*	***Hyphenweb***: intradermal venectasis
	2*	***Reticular varices:*** dilated tortuous veins, not belonging to the main trunk or its major branches
	3*	***Trunk varices***: dilated, tortuous trunks of the long or short saphenous vein and their branches of the first or second order
		Chronic venous insufficiency: Categorised into grades I, II and II according to the presence of dilated subcutaneous veins, skin changes and ulceration.

* Each category is graded 1-3 according to the degree and extent of tortuosity and prominence.

APPENDIX 3: CEAP CLASSIFICATION OF CHRONIC VENOUS DISEASE

The CEAP is based on clinical signs (C), etiology (E), anatomic distribution of disease (A) and underlying pathophysiologic findings (P).

CLASS	**CLINCAL SIGNS**
C0	No visible or palpable signs of venous disease.
C1	Telangiectases or reticular veins.
C2	Varicose veins (diameter of 3mm or more).
C3	Oedema or corona
C4a	Skin changes (pigmentation, venous eczema)
C4b	Skin changes (lipodermatosclerosis, atrophie blanche)
C5	Skin changes as defined above with healed ulceration
C6	Skin changes as defined above with active ulceration

DEFINITION

C1 Telangiectases:	Permanently dilated intradermal venules less than 1mm in size (also called spider veins and thread veins).
C1 Reticular veins:	Permanently dilated bluish subdermal vein, usually 1mm to less than 3mm in diameter.
C2 Varicose veins:	Subcutaneous dilated vein 3mm in diameter or larger, measured in upright position.
C3 Corona:	Fan-shaped pattern of numerous small intradermal veins on the medial or lateral aspects of the ankle and foot.
C3 Oedema:	Perceptible increase in volume of fluid in subcutaneous tissue characterised by indentation with pressure, usually occurring in the ankle region.
C4a Pigmentation:	Brownish darkening of the skin. Usually occurs in the ankle region but may extend to the leg and the foot. An early skin change.
C4a Eczema:	Dermatitis which may progress to blistering, weeping or scaling eruption of the skin of the leg. Often located near varicose veins but may be located anywhere in the leg. Usually caused by chronic venous insufficiency.
C4b Lipodermatosclerosis:	Localised chronic inflammation of the skin and subcutaneous tissue, sometimes associated with scarring. Acute inflammation and tenderness. Sign of severe venous disease.
C4b Atrophie blanche:	Localised, often circular whitish and atrophic skin areas surrounded by dilated capillary spots. Sign of severe CVD, and not to be confused with healed ulcer scars. Scars of healed ulceration may also exhibit atrophic skin with pigmentary changes, but are distinguishable by history of ulceration.
C5 + C6 Ulcer	Full thickness chronic defect of skin, most frequently in ankle region, that fails to heal spontaneously.

APPENDIX 4: VENOUS SEVERITY SCORING SYSTEM (VSSS)

VENOUS CLINICAL SEVERITY SCORE (VCSS)

ATTRIBUTE	ABSENT = 0	MILD = 1	MODERATE =2	SEVERE = 3
Pain	None	Occasional, not restricting activity or requiring analgesics	Daily, moderate activity limitation, occasional analgesics	Daily, severe limiting activities or requiring regular use of analgesics
Varicose veins [a]	None	Few, scattered, isolated branch VVs	Multiple: single segment GS or LS distribution involving calf only	Extensive: multi segmental GS and LS distribution, involving calf and thigh
Venous oedema [b]	None	Evening ankle oedema only	Afternoon oedema, above ankle	Morning oedema above ankle requiring activity change
Skin pigmentation [c]	None or focal, low intensity (tan)	Diffuse, but limited tin area and old (brown)	Diffuse over most of gaiter distribution (lower 1/3) or recent pigmentation (purple)	Wider distribution (above lower 1/3) and recent pigmentation
Inflammation	None	Mild cellulitis, limited to marginal area around ulcer	Moderate cellulitis, involves most of gaiter area (lower 1/3)	Severe cellulitis (lower 1/3 and above) or significant venous eczema
Induration	None	Focal, circum-malleolar (≤5 cm)	Medial or lateral, less than lower third of leg	Entire lower third of leg or more
No. of active ulcers	0	1	2	≥ 2
Active ulceration, duration	None	< 3 months	>3 months, < 1 years	Not healed > 1 year
Active ulcers, size [d]	None	< 2 cm diameter	2-6 cm diameter	> 6 cm diameter
Compressive therapy [e]	Not used or not compliant	Intermittent use of stockings	Wears elastic stockings most days	Full compliance: stockings + elevation

[a] "Varicose" veins must be > 4 mm diameter so that differentiation is between C1 and C2 venous pathology.
[b] Presumes venous origin by characteristics eg, Brawny (not pitting or spongy) oedema, with significant effect of standing/limb elevation and/or other clinical evidence of venous aetiology, ie, varicose veins. Oedema must be regular finding, eg, daily occurrence. Occasional or mild oedema does not qualify
[c] Focal pigmentation over varicose veins does not qualify
[d] Largest diameter/diameter over largest ulcer

VENOUS SEGMENTAL DISEAESE SCORE (VSDS)

	REFLUX		**OBSTRUCTION †**
½	Lesser saphenous		‡
1	Greater saphenous	1	Greater saphenous (only if thrombosed or previously excised in association with superficial femoral-popliteal occlusion)
½	Perforators, thigh		‡
1	Perforators, calf		‡
2	Calf veins, multiple (PT alone = 1)	1	Calf veins, multiple
2	Popliteal vein	2	Popliteal vein
1	Superficial femoral vein	1	Superficial femoral vein
1	Profunda femoris vein	1	Profunda femoris vein
1	Common femoral vein	2	Common femoral vein
		1	Iliac vein
		1	Inferior vena cava
10	Maximum reflux score §	10	Maximum obstruction score §

As determined by appropriate venous imaging (phlebography or Duplex scan)
† The excision, ligation, or traumatic obstruction of deep venous segments counts toward obstruction points just as much as their thrombosis
‡ Normally there are no valves above the CFV so no reflux points are assigned to them. In addition, perforator interruption and saphenous ligation/excision (with the single exception noted) do not count in the obstruction score, but as a reduction of the reflux score
§ Not all of the 11 segments can be involves in reflux or obstruction. 10 is the maximum score which can be assigned, and this might be achieved by complete reflux at all segmental level
Taken from Rutherford 2000

VENOUS DISABILITY SCORE (VDS)

0	asymptomatic
1	Asymptomatic but able to carry out usual activities* without compressive therapy
2	Can carry out usual activities* only with compression and/or limb elevation
3	Unable to carry out usual activities* even with compression and/or limb elevation

*Usual activities = patient activities before onset of disability from venous disease
Taken from Rutherford 2000

1

APPENDIX 5: LETTER OF INVITATION TO FOLLOW UP

Study no:

Name
Address

Date

Dear

Research project: Edinburgh Vein Study

In 1994-1996 you very kindly participated in our research study and had a clinical examination of your legs in the University of Edinburgh. We are writing to invite you to take part in a follow-up study to try and find out more about the on-going state of health of veins in the legs as people get older.

The first stage of the study in which you took part was extremely successful resulting in worldwide interest in our findings on the causes of diseases affecting veins in the leg. Enclosed is a copy of the newsletter with the main results from the first stage. This follow up study will also provide new and important information which will lead to a greater understanding of how we can prevent venous diseases and their serious complications in the future.

Taking part in the study will require you to attend an appointment on one occasion to have an examination of the veins in your legs. These tests are painless and do not involve any foreseeable risk. Appointments will be held at the Wellcome Trust Clinical Research Facility at the Western General Hospital, Edinburgh. More detailed information is given in the accompanying patient information sheet.

We are able to arrange an appointment at a time convenient for you. We can reimburse travel and accommodation expenses from within the UK and, if appropriate, provide assistance in seeking and taking time off work. We will also advise your General Practitioner of any clinically significant information that comes to light.

We very much hope you will accept our invitation to take part in this research and would be grateful if you would return the enclosed reply slip in the pre-paid envelope. We will then contact you at a later date to arrange an appointment.

If you would like any further information, please do not hesitate to contact the study co-ordinator, Miss Lindsay Robertson, by telephone 0131 650 4555 or e-mail Edinburghveinstudy@ed.ac.uk.

Yours Sincerely

Lindsay Robertson

APPENDIX 6: PATIENT INFORMATION SHEET

EDINBURGH VEIN STUDY
PARTICIPANT INFORMATION SHEET

Title of study: Lifestyle and clinical factors determining progression of venous disease in the legs: Edinburgh Vein Study.

In 1994-1996 you very kindly participated in the Edinburgh Vein Study and had a clinical examination of your legs in the University of Edinburgh. You are being invited to take part in a follow-up study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and talk to others about the study if you wish. Ask us if there is anything that is unclear or if you would like more information.

What is the purpose of the study?

Diseases of veins in the legs are very common affecting about one third of the adult population. We know very little about how and why people develop varicose veins over time and why some patients develop serious complications such as a leg ulcer. This study will address these questions and the results will help us lead to the development of measures to prevent this condition and its complications in the future.

Why have I been chosen?

You were one of the 1566 original participants in the Edinburgh Vein Study. We would like to examine you again as part of the follow-up study to review your condition. Since this is a follow up study, we would like to examine everyone who participated originally. It is equally important for us to examine you whether or not you have had varicose veins.

Do I have to take part?

Taking part is entirely your own decision. If you decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form when you attend for your examination. At any time during the examination, you are free to withdraw without having to give a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you normally receive.

What will happen to me if I take part?

You will be invited to attend the Wellcome Trust Clinical Research Facility at the Western General Hospital, Edinburgh on one occasion only for a detailed examination of the veins in your legs. The tests are painless and do not involve any risk. No injections or blood tests are carried out.

You will have an ultrasound scan of your legs so that we can see the blood flowing in your veins. The scan is performed while you are in a standing position, but resting against a bed which is tilted at an angle. Gel needs to be applied to the skin of your leg. This may feel cold and sticky but not unpleasant. Your calf and thigh muscles will be squeezed gently to see in which direction the blood is flowing. The scan is not painful but does require you to be still for a short period of time. If you feel tired at any time, you can rest and restart when you feel ready.

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 and asked to fill in a questionnaire about your past medical history, smoking and exercise etc. If you are unsure of any of the questions, you can discuss this with the research staff at your appointment at the clinic. The appointment should take around one hour. Refreshments will be served during your visit.

What do I have to do?

There are no special arrangements for the examination. You would simply have to attend an appointment at the Wellcome Trust Clinical Research Facility at the Western General Hospital, Edinburgh. Ideally you should wear loose or easily removable clothing below the waist. We shall pay any travel and accommodation expenses which you incur.

What are the possible disadvantages and risks of taking part?

There are no foreseeable risks in taking part in this study. You will be required to stay reasonably still for about half an hour during the scan but you will be free to move around at any time if you feel the need.

What are the possible benefits of taking part?

There are no direct benefits to you in taking part as the investigations are unlikely to affect any treatment you are having. The research should hopefully benefit others in the future by identifying measures to prevent venous disease.

Will my taking part in the study be kept confidential?

Yes. All information which is collected about you during the course of the research will be kept strictly confidential and will only be available to the principal researchers. The information is essentially of a technical nature understood by specialists. Your General Practitioner will be informed of any clinically significant results.

What will happen to the results of the research study?

The results of the study will not be able to identify any individual patient. The results will be published in medical scientific journals and a report sent to the Scottish Executive. We shall send you a newsletter describing the results in due course.

Who is organising and funding the research?

The study is being organised by the Wolfson Unit for Prevention of Peripheral Vascular Diseases in the University of Edinburgh. The study is being funded by the Chief Scientist Office in the Scottish Executive.

Who has reviewed this study?

This study has been reviewed and approved by independent referees approved by the Chief Scientist Office and by the Lothian Health Research Ethics Committee.

Contact for further information

Miss Lindsay Robertson
Wolfson Unit for Prevention of Peripheral Vascular Diseases
Public Health Sciences
University of Edinburgh
Teviot Place
Edinburgh
EH8 9AG
Tel: 0131 650 4555
E-mail: Lindsay.Robertson@ed.ac.uk

We hope that you will agree to take part in this study and if so, you will be given a copy of the information sheet and a signed consent form to keep.

Thank you

APPENDIX 7: PARTICIPANT NEWSLETTER

EDINBURGH VEIN STUDY

MAIN RESULTS

- Varicose veins occur in around one third of men and women aged 18-64 years.
- Small 'spidery' varicose veins occur in over 80% of the population.
- The presence of varicose veins increases with age and occurs equally in all socioeconomic groups.
- Varicose veins, especially mild ones, are slightly more common in men than in women. Earlier studies suggested that men were not affected so much, but perhaps changes in lifestyle are increasing the risk for men.
- Individuals with varicose veins are more likely to have disturbances in blood flow in their leg.
- In men, these disturbances in flow are more likely to affect the deep veins in the leg, while in women the veins nearer the surface are more likely to be affected.
- Individuals with varicose veins are only slightly more likely to experience symptoms in their legs, such as heaviness, aching and itching than people without varicose veins.
- The occurrence of varicose veins in women is not strongly related to number of previous pregnancies.
- There is no strong link between the amount of fibre consumed in the diet, different bowel habits and risk of developing varicose veins.
- The risk of having varicose veins is related to some underlying differences in certain
- factors involved in blood clotting

These results are important in helping us to build up a picture of the frequency of varicose veins in the population and in understanding why they occur. However, more research is still required. The follow-up study we are conducting will help us to understand why people develop varicose veins and identify steps to try and prevent their occurrence.

APPENDIX 8: REPLY FORM

EDINBURGH VEIN STUDY

Please complete and return in the pre-paid envelope

Name .....

Address .....

.....

Postcode .....

Telephone .....

E-mail address .....

I would like to take part in the Edinburgh Vein Study follow-up: *Please tick one box*

☐ Yes ☐ No

☐ If you would like more information first:

Please contact:

Miss Lindsay Robertson
Wolfson Unit for Prevention of Peripheral Vascular Disease
Public Health Sciences
University of Edinburgh
Teviot Place
Edinburgh
EH8 9AG
Tel: 0131 650 4555
E-mail:Lindsay.Robertson@ed.ac.uk

APPENDIX 9: CONFIRMATION LETTER

Name
Address

Date

Dear Name

Research project: Edinburgh Vein Study

Further to our recent telephone conversation, I am writing to confirm that your appointment for the Edinburgh Vein Study has been arranged for (insert date) at the Wellcome Trust Clinical Research facility, Western General Hospital, Edinburgh. I have enclosed a map to help you find your way to the clinic. The examination will take approximately one hour fifteen minutes. Please note that you may withdraw at any point during the examination if you wish so. I shall be pleased to reimburse any travelling expenses that you incur.

I also enclose a study questionnaire and would be grateful if you could complete as much of it as you can and take it with you to the appointment. If you have difficulty in answering any of the questions, you can discuss them with the study nurses at the clinic.

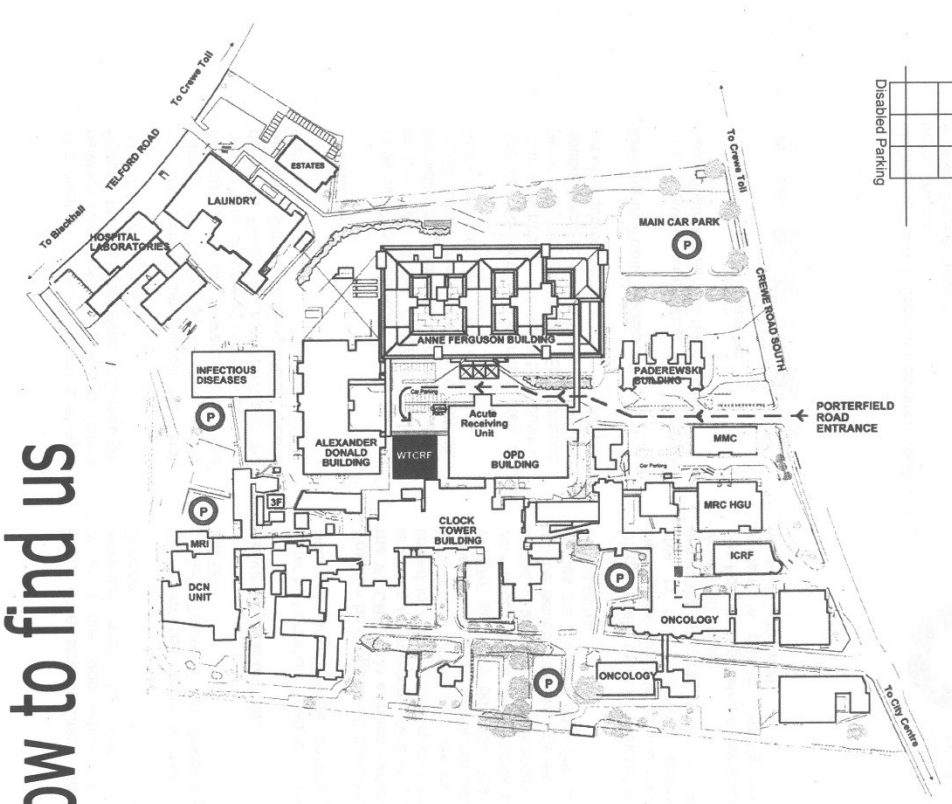
If this appointment becomes unsuitable for any reason, please telephone a member of the study team on 0131 650 4555 to arrange an alternative time.

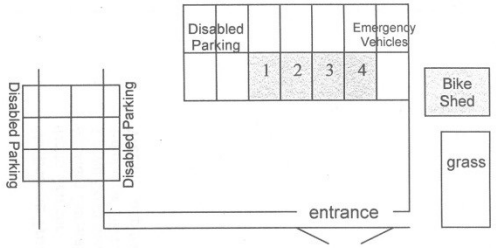
Yours Sincerely,

Miss Lindsay Robertson
Study co-ordinator

APPENDIX 10: MAP OF THE RESEARCH CLINIC

how to find us





Attending Research Clinic:

- On Ground Floor.
- Report to Clinic Reception and/or wait in the waiting area.

Attending Research Ward:
(including day studies)

- On First Floor.
- Access by lift or stairs.
- Report to Ward Reception and/or wait in the waiting area.

Enquiries Tel: 0131 537 3387

The Wellcome Trust Clinical Research Facility (WTCRF) main entrance is on the ground floor, off the north corridor between the Acute Receiving Unit (ARU) and the Alexander Donald Building (ADB).

The Western General Hospital is situated between Crewe Road South and Telford Road in the Craigleith area of Edinburgh. Map of North Edinburgh.

The Wellcome Trust Clinical Research Facility (WTCRF) is a three-storey building. The main entrance is on the ground floor, off the north corridor between the Acute Receiving Unit (ARU) and the Alexander Donald Building (ADB). Please see map.

Directions:

Enter via Porterfield Road; follow the road to the right of the Outpatient building towards the Alexander Donald Building (ADB), under the walkway and past the Acute Receiving Unit (ARU) on the left.

The WTCRF entrance is immediately on your left opposite the large blue building (Anne Ferguson Building). Enter through double glass doors and through the next set of turquoise doors.

Arriving by Public Transport:

The following buses stop at the Crewe Road South entrance to the hospital:

Lothian Regional Transport

19 19A 29 37 37A X37 42

Buses either stop on Crewe Road South or at a bus stop within the hospital grounds, near the Anne Ferguson Building.

For information about all bus services, contact Traveline on freephone 0800 232323.

Arriving by Car or Taxi:

Enter by Porterfield Road, off Crewe Road South, as above. Please see map.

You can be dropped off directly outside the WTCRF main entrance where there is space for turning. WTCRF parking is limited to 4 designated spaces directly in front of the building, for use by subjects taking part in studies. Please contact the WTCRF secretary on 0131 537 2591 if your circumstances necessitate provision of one of these reserved spaces. Permits will be issued, however please note that spaces are allocated on a first come first served basis.

Unfortunately, there is restricted parking in the hospital grounds so you may not be able to find a parking space easily especially at peak times (8.45am-3pm Monday to Friday).
The hospital operates a pay and display system in public parking areas, as marked on the map.

Wellcome Trust | Clinical Research Facility
North Corridor
Western General Hospital
Crewe Road South
Edinburgh, EH4 2XU
Website: http://www.wtcrf.ed.ac.uk

clinical research facility EDINBURGH

APPENDIX 11: STUDY QUESTIONNAIRE

Study no: ……

EDINBURGH VEIN STUDY

QUESTIONNAIRE

The information you give in this questionnaire will be treated as **strictly confidential** and will only be seen by the study team The results of the research will appear only in the form of general statistics from which it will be impossible to identify you as an individual.

Please complete the following:

SURNAME: .....

FORENAMES: .....

DATE: .....

Please complete this questionnaire and bring it along with you to your appointment.

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

THANK YOU FOR YOUR CO-OPERATION IN THE STUDY.

Study no: ……

PERSONAL DETAILS

1. Please tick one Male ☐ Female ☐

2. What is your date of birth?

Day		Month		Year	

GENERAL HEALTH

3. In general, would you say your health is: (*Please tick **one** box*)

Excellent ☐ Fair ☐

Very good ☐ Poor ☐

Good ☐

4. **Compared to one year ago**, how would you rate your health in general **now**? (*Please tick **one** box*)

Much better than one year ago ☐
Somewhat better than one year ago ☐
About the same as one year ago ☐
Somewhat worse than one year ago ☐
Much worse than one year ago ☐

5. The following questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

*(Please tick **one** box for each statement*)

	Yes, limited a lot	**Yes, limited a little**	**Not limited at all**
5a. **Vigorous activities**, such as running, lifting heavy objects or strenuous sports	☐	☐	☐
5b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
5c. Lifting or carrying groceries	☐	☐	☐
5d. Climbing **several** flights of stairs	☐	☐	☐
5e. Climbing **one** flight of stairs	☐	☐	☐
5f. Bending, kneeling, or stooping	☐	☐	☐
5g. Walking **more than a mile**	☐	☐	☐
5h. Walking several hundred yards	☐	☐	☐
5i. Walking 100 yards	☐	☐	☐
5j. Bathing or dressing yourself	☐	☐	☐

6. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(*Please tick **one** box for each statement*)

	Yes	**No**
6a. Cut down on the **amount of time** you spent on work or other activities	☐	☐
6b. Accomplished less than you would like	☐	☐
6c. Were **limited** in the **kind** of work or other activities	☐	☐
6d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	☐	☐

7. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotion problems** (e.g. feeling depressed or anxious)?

(*Please tick **one** box for each statement*)

	Yes	**No**
7a. Cut down on the **amount of time** you spent on work or other activities	☐	☐
7b. Accomplished less than you would like	☐	☐
7c. Didn't do work or other activities as **carefully** as usual	☐	☐

8. During the **past 4 weeks**, to what extent has your physical or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

(*Please tick **one** box*)

Not at all	☐	Quite a bit	☐
Slightly	☐	Extremely	☐
Moderately	☐		

9. How much **physical** pain have you had during the **past 4 weeks**? (*Please tick **one** box*)

None	☐	Moderate	☐
Very mild	☐	Severe	☐
Mild	☐	Very severe	☐

10. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)? (*Please tick **one** box*)

Not at all	☐	Quite a bit	☐
A little bit	☐	Extremely	☐
Moderat	☐		

11. These questions are about how you feel and how things have been with you **during the past 4 weeks**. Please give the one answer that is closest to the way you have been feeling for each item.

*(Please tick **one** box for each statement)*

	All of the time	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
11a. Did you feel full of life?	☐	☐	☐	☐	☐	☐
11b. Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
11c. Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
11d. Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
11e. Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
11f. Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
11g. Did you feel worn out?	☐	☐	☐	☐	☐	☐
11h. Have you been a happy person?	☐	☐	☐	☐	☐	☐
11i. Did you feel tired?	☐	☐	☐	☐	☐	☐

12. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives etc.) (*Please tick **one** box*)

All of the time ☐

Most of the time ☐

Some of the time ☐

A little of the time ☐

None of the time ☐

13. How TRUE or FALSE is **each** of the following statements for you?

*(Please tick **one** box for each statement)*

	Definitely true	**Mostly true**	**Don't know**	**Mostly false**	**Definitely false**
13a. I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
13b. I am as healthy as anybody I know	☐	☐	☐	☐	☐
13c. I expect my health to get worse	☐	☐	☐	☐	☐
13d. My health is excellent	☐	☐	☐	☐	☐

LEG PROBLEMS

14. During the **past 4 weeks**, how often have you had any of the following leg problems?

(*Please tick **one** box for each statement)*

	Every day	**Several times a week**	**About once a week**	**Less than once a week**	**Never**
14a. Heavy legs	☐	☐	☐	☐	☐
14b. Aching legs	☐	☐	☐	☐	☐
14c. Swelling	☐	☐	☐	☐	☐
14d. Night cramps	☐	☐	☐	☐	☐
14e. Heat or burning sensation	☐	☐	☐	☐	☐

	Every day	Several times a week	About once a week	Less than once a week	Never
14f. Restless legs	☐	☐	☐	☐	☐
14g. Throbbing	☐	☐	☐	☐	☐
14h. Itching	☐	☐	☐	☐	☐
14i. Tingling sensation (e.g. pins and needles)	☐	☐	☐	☐	☐

15. At what time of day is your leg problem **most intense**?

On waking	☐	During the night	☐
At mid-day	☐	At any time of day	☐
At the end of the day	☐	Never	☐

16. **Compared to one year ago**, how would you rate your leg problem in general **now**?

- Much better than one year ago ☐
- Somewhat better than one year ago ☐
- About the same now as one year ago ☐
- Somewhat worse than one year ago ☐
- Much worse now than one year ago ☐
- I did not have any leg problem last year ☐

17. The following items are about activities that you might do in a typical day. Does your **leg problem now limit you** in these activities? If so, how much?

*(Please tick **one** box for each statement)*

	I do not work	YES, limited a lot	YES, limited a little	NO, Not limited at all
17a. Daily activities at work	☐	☐	☐	☐
17b. Daily activities at home (e.g. housework, ironing, odd jobs, gardening)		☐	☐	☐
17c. Social or leisure activities in which you are **standing** for long periods of time (e.g. shopping, public transport)		☐	☐	☐
17d. Social or leisure activities in which you are **sitting** for long periods of time (e.g. cinema, theatre, travelling)		☐	☐	☐

18. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your leg problem?**

	Yes	No
Cut down the amount of time you spent on work or other activities	☐	☐
Accomplished less than you would like	☐	☐
Were limited in the kind of work or other activities	☐	☐
Had difficulty performing the work or other activities (e.g. it took extra effort)	☐	☐

19. During **the past 4 weeks**, to what extent has your leg problem interfered with your normal social activities with family, friends, neighbours or groups?
*(Please tick **one** box)*

Not at all	☐	Quite a bit	☐
Slightly	☐	Extremely	☐
Moderately	☐		

20. How much leg pain have you had during the **past 4 weeks**? (*Please tick **one** box)*

None	☐	Moderate	☐
Very mild	☐	Severe	☐
Mild	☐	Very severe	☐

21. These questions are about how you feel and how things have been with you **during the past 4 weeks as a result of your leg problem**. For each question, please give one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks** –

(*Please tick **one** box for each statement)*

	All of the time	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
21a. Have you felt concerned about the appearance of your leg(s)?	☐	☐	☐	☐	☐	☐
21b. Have you felt irritable?	☐	☐	☐	☐	☐	☐
21c. Have you felt a burden to your family or friends?	☐	☐	☐	☐	☐	☐

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
21d. Have you been worried about bumping into things?	☐	☐	☐	☐	☐	☐
21e. Has the appearance of your leg(s) influenced your choice of clothing?	☐	☐	☐	☐	☐	☐

YOUR HEALTH

22. Have you ever been told by a doctor that you had any of the following?

		Left Leg	Right Leg	No
a.	Varicose veins	☐	☐	☐
b.	Leg ulcer	☐	☐	☐
c.	Phlebitis / vein inflammation	☐	☐	☐
d.	Swollen leg either i) following pregnancy	☐	☐	☐
	ii) following operation	☐	☐	☐
	iii) other (specify) _____			
e.	White leg of pregnancy	☐	☐	☐
f.	Deep vein thrombosis (clot in the leg)	☐	☐	☐
g.	Fractured / broken leg	☐	☐	☐

		Yes	No
h.	Hernia (lump in the groin)	☐	☐
i.	Pulmonary embolism (clot on the lung)	☐	☐
j.	Arthritis	☐	☐

FAMILY HISTORY

23. Have any of these members of your family suffered from the following? (Please **tick**)

	Varicose veins	Leg ulcer
Mother	☐	☐
Father	☐	☐
Brother / sister	☐	☐
Grandparents	☐	☐
Other relatives (please specify)	_____	_____

VARICOSE VEINS

If you have not had varicose veins, then women go to question 27 and men go to question 31a.

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

25. Have you had the following treatments for varicose veins? (Please **tick**)

		Left Leg	Right Leg	No
a.	Operation	☐	☐	☐
b.	Injection of veins	☐	☐	☐
c.	Compression (stockings, bandaging)	☐	☐	☐

If you have <u>never</u> had an operation or injections for your varicose veins (i.e. you answered <u>no</u> to questions 25 a and b, then women go to question 27 and men go to question 31a.

26a. Have your varicose veins come back since they were first treated

Yes ☐ No ☐

If **<u>yes</u>**, how soon after treatment did they come back? Years Months

26b. Have you had your varicose veins treated by operation or injection more than once?

Yes ☐ No ☐

26c. In which hospitals have you had treatment for varicose veins?

Hospital Year (approximately)

WOMEN'S REPRODUCTION

Men omit this section and go to Question 31a

27. What age did you go through:

Menarche (i.e. started your periods) ☐ years

Menopause (i.e. periods stopped) ☐ years

(if you are still having periods, put a 0 in the box)

28a. Are you pregnant at the moment? Yes ☐ No ☐

28b. How many times have you been pregnant? (include any current pregnancy and miscarriages)

☐ times

28c. Did any varicose veins first develop during pregnancy? Yes ☐ No ☐

If you've never had varicose veins please tick here ☐

28d. If yes, during which pregnancy did they develop? ☐ pregnancy

29a. Have you ever been on the Oral Contraceptive Pill? Yes ☐ No ☐

If yes, for how many years in total? ☐ years

29b. Are you currently on the Oral Contraceptive Pill? Yes ☐ No ☐

If yes, what is the name of the pill? _____

(If you don't know the exact name, do you take it **<u>every</u>** day or do you only take it 3 weeks out of 4?)

Everyday ☐ 3 out of 4 weeks ☐

30a. Have you ever been on Hormone Replacement Therapy (HRT)? Yes ☐ No ☐

If yes, for how many years in total ☐ years

30b. Are you currently on Hormone Replacement Therapy (HRT)? Yes ☐ No ☐

If yes, what is the name of the tablets you take and /or the patches you wear? _____

SMOKING

31a. Do you smoke at present? Yes ☐ No ☐

If no, proceed to 31f

31b. What do you usually smoke now?

Cigarettes ☐

Pipe ☐

Cigars ☐

If only pipes or cigars, proceed to 31f

31c. How many cigarettes do you usually smoke now? ☐ cigarettes per day

31d. For how many years of your life have you smoked cigarettes? ☐ years

31e. How many cigarettes have you smoked per day on average during the period you have smoked?

☐ cigarettes per day

Now proceed to 31j.

31f. Have you ever smoked cigarettes regularly? Yes ☐ No ☐

If no, proceed to 31j.

31g. How many cigarettes per day did you smoke on average while you were a smoker?

☐ cigarettes per day

31h. For how many years did you smoke cigarette ☐ years

31i. How long is it since you gave up smoking cigarettes? ☐ years

31j. Are you exposed to cigarette smoke at home or at work? Yes ☐ No ☐

PHYSICAL EXERCISE

The following section gives examples of the sort of activities you might do now.

Light activity	**Moderate activity**	**Strenuous activity**
Ballroom dancing	Badminton	Basketball
Bowling	Cricket	Competitive cycling
Light DIY	Cycling (to work, shops etc)	Competitive swimming
Light gardening	Heavy DIY	Competitive running
Horse riding	Golf	Field sports
Sailing	Jogging	Sports training
Walking (to work, shops etc)	Swimming	Squash
Yoga	Tennis	Football
Other activities of similar intensity	Other activities of similar intensity	Other activities of similar intensity
Please specify others	Please specify others	Please specify others
_____	_____	_____

32. In a **typical week during the last year**, on how many occasions would you take part **for more than 20 minutes each time**:

Insert **none** if appropriate

In **light** activity? times (see above)	In summer	_____
	In winter	_____
In **moderate** activity times (see above)	In summer	_____
	In winter	_____
In **strenuous** activity times (see above)	In summer	_____
	In winter	_____

33. Which of the following best describes your **daily work or other daytime activity** at the **present time**?

(*Please tick **one** box only*)

I am usually sitting during the day and do not walk about much	☐	e.g. office workers, drivers
I stand or walk quite a lot during the day, but do not have to carry of lift things very often	☐	e.g. housewives, shop assistants
I usually lift or carry light loads and have to climb stairs and /or hills often	☐	e.g. postmen, packers
I do heavy work and carry heavy loads	☐	e.g. building, mining and agricultural workers

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

APPENDIX 12: NON-PARTICIPANT QUESTIONNAIRE

Dear Name

Research project: Edinburgh Vein Study

Sometime during the past three months you received an invitation to take part in the Edinburgh Vein Study. We understand that you decided not to do so.

The Edinburgh Vein Study is one of the most important of its kind to be carried out in the UK. The results of the study, conducted in 1992-1994, were published in scientific papers and you may have seen some that were presented in a BBC Healthcheck Watchdog programme. The follow-up study will provide important information about the ongoing state of health of veins in the legs as people get older.

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.**

We 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,

Lindsay Robertson

Miss Lindsay Robertson
Research Fellow

Professor erry Fowkes
Professor of Epidemiology

Study Number …….

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:

Please fill in this form by ticking the appropriate boxes.

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

	Yes	No
Varicose veins	☐	☐
Leg ulcer	☐	☐
Vein inflammation/phlebitis	☐	☐

	Yes	No
2. Do you think you have varicose veins?	☐	☐

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

	Yes	No
Operation	☐	☐
Injection of veins	☐	☐
Stockings/bandages	☐	☐

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

Not interested in study	☐
Study waste of time	☐
Too busy	☐
Clinic times inconvenient	☐
Worried about examination or results	☐
Housebound	☐
Feel unhealthy so don't need to take part	☐
Already seeing doctor about veins	☐
Forgot about invitation/appointment	☐
Object to invasion of privacy	☐
Other (please give details)	☐

Thank you very much for filling in this form.

APPENDIX 13: CONSENT FORM

Study Number……..

CONSENT FORM

Title of Study: Edinburgh Vein Study – lifestyle and clinical factors determining progression of venous disease in the legs.

Name of Researcher: Miss Lindsay Robertson
Wolfson Unit for Prevention of Peripheral Vascular Diseases
Public Health Sciences
University of Edinburgh
Teviot Place
Edinburgh
EH8 9AG
Tel: 0131 650 4555

Please initial

1. I confirm that I have read and understood the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ……
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ……
3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by the principal investigators or by regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ……
4. I agree to have my legs photographed for the purpose of the study. ……
5. I understand that my General Practitioner will be informed of any clinically significant information that comes to light as a result of this study. ……
6. I agree to take part in the above study. ……

……	……	……
Name of participant	**Date**	**Signature of participant**
……	……	……
Name of investigator	**Date**	**Signature of investigator**

When completed, once copy to be given to participant, one to be kept in the participant's study file.

APPENDIX 14: STUDY RECORDING FORMS

Participant name…… *Study Number……..*

EDINBURGH VEIN STUDY

HEIGHT AND WEIGHT RECORDING FORM

	Day	Month	Year
Date of examination	…… /	…… /	…….

Time of examination …… **am / pm**

HEIGHT (without shoes) ☐☐☐ . ☐ **cms**

WEIGHT (without shoes) ☐☐☐ . ☐ **kgs**

BMI ☐☐ . ☐ **kg/m^2**

PARTICIPANT'S ETHNIC ORIGIN:

White Caucasian	☐	Chinese	☐
African	☐	Other	……
Indian	☐		

Examined by:

A.B. *S.B* *L.R* *H.S*

Participant 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

	RIGHT		**LEFT**	
PROCEDURES	**Operations**	**Injections**	**Operations**	**Injections**
Great saphenous vein	YES / NO	YES / NO	YES / NO	YES / NO
Small saphenous vein	YES / NO	YES / NO	YES / NO	YES / NO

	REFLUX					
	RIGHT			**LEFT**		
	Measure 1 (s)	Measure 2 (s)	Other	Measure 1 (s)	Measure 2 (s)	Other
DEEP						
CFV						
FV origin						
FV lower 1/3						
POP above knee						
POP below knee						
SUPERFICIAL						
GSV origin						
GSV lower 1/3 thigh						
GSV upper calf						
GSV lower calf						
SV						

N.S = not seen **No flow** = no flow

COMMENTS: .....

.....

Examined by:
A.B. *S.B* *L.R* *H.S*

Participant name……. *Study number……*

EDINBURGH VEIN STUDY

LEG EXAMINATION FORM

	BACK OF LEGS		FRONT OF LEGS	
	LEFT	**RIGHT**	**LEFT**	**RIGHT**
C0 **Venous disease**				
C1a **Telangiectases (1,2,3)**				
C1b **Reticular varices (1,2,3)**				
C2 **Trunk varices (1,2,3)**				
C3 **Oedema**				
C3 **Corona**				
C4a[1] **Pigmentation**				
C4a[2] **Eczema**				
C4b[1] **Lipodermatosclerosis**				
C4b[2] **Atrophie blanche**				
C5 **Healed ulcer**				
C6 **Active ulcer**				

0 = No **1 =** Yes

COMMENTS: .....

.....

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

Number of standard photographs taken: 3 / 6 / _____ if other, specify the number

Specify any problems with the photography:

.....

Examined by:

A.B. *S.B* *L.R* *H.S*

APPENDIX 15: DUPLEX ULTRASOUND SCANNING PROTOCOL

EDINBURGH VEIN STUDY

SCANNING PROTOCOL

OBJECTIVE

To identify points and patterns of venous reflux in the deep and superficial veins of the legs.

PREPARATION

1. Make sure the probe is clean. Set the rapid air source to a pressure of 110 mmHg.
2. The scanner is set up so that all scans are conducted within the venous section of the peripheral vascular protocol. If the setup is changed, use the SCANHEAD button to bring up the protocols. Select the L7-438mm probe, "peripheral vascular" and "venous".
3. Enter the participant's name, study ID no and date of birth using the PATIENT DATA button and save.
4. Explain the procedure to the patient. Document any previous blackouts, medication for high blood pressure or medical conditions. Ask them to notify you immediately if they feel faint. Ask the patient to disrobe from the waist down.
5. The participant should be asked to lie flat on the tilt-table with one pillow under their head. Once they are comfortable, the tilt-table should be raised in a reverse fashion to a near-standing position (45°). For participants who find it difficult to weight-bear for long periods, the tilt-table can be reduced to a 30° angle. If the participant is unable to tolerate this then the scan should be abandoned since significant reflux may not be observed if the angle is <30°. The participant should then be encouraged to take most of their weight on their opposite leg with the leg to be scanned relaxed to the side with the knee slightly bent.

HOLDING THE PROBE

It is important to hold the probe the correct way. If scanning in transverse, the leading edge should always be to the participant's right hand side i.e. facing you. If scanning longitudinally, the leading edge should be pointing towards the participant's heart. When not using the probe (i.e. between reflux measurements), take it down and place it back on the stand in order to give the hand and arm a break.

IMAGING THE VEINS

Start by measuring the deep veins:

Deep veins:

Each deep vein (CFV, FV and POP) is accompanied by its artery. The artery usually lies underneath the vein but it is vital to check this. Locate deep veins in transverse view in black and white. Use the colour function to check for venous or arterial blood flow. This button shows the flow of blood in the veins as blue and the flow of blood in the arteries as red. Squeeze the calf to initiate flow. If you are on the vein, you should see a short burst of blue representing the blood being squeezed out. If you see red, you are focussing on the artery and will need to readjust the probe until you are satisfied that you are on the vein.

6. Begin in cross-section by imaging the sapheno-femoral junction (SFJ), also known as the "Mickey Mouse" configuration. Note that in patients who have had varicose vein surgery, the GSV may not be present if it has been previously tied or stripped.
7. Check for a thrombus by pushing the probe (perpendicular to the body) firmly until the vein walls collapse completely (arteries cannot be compressed so the CFA will remain open). If the walls cannot be compressed, the patient may have had a thrombus in their leg (invite back for a second scan with Paul Allan).
8. Still in a longitudinal view, move the probe upwards until you can see the CFV just above the SFJ.
9. Take a measurement of reflux. Go into colour flow and pulsed Doppler mode. Place the Doppler cursors on the walls of the vein segment. Inflate the pneumatic cuff to the pre-set pressure of 110 mmHg. Check that the compression augments venous outflow and observe for signs of reflux. Measure the reflux time by placing the calipers at the start and end of the spectra. Wait a minimum of 5 seconds between calf compressions to take another reflux measure. Record both reflux times.
10. Move the probe down until you can see the SFV 2cm below the SFJ. Take 2 measurements of reflux (Step 9).
11. Follow the SFV down to the lower third of the thigh and take 2 measurements of reflux (Step 9)

12. Ask the patient to turn towards you in order for you to scan the popliteal (POP) vein behind the knee. In transverse view, image the sapheno-popliteal junction (SPJ). Note that in patients you have had varicose vein surgery, the SSV may be missing.
13. Turn the probe longitudinally and move upwards so that you can image the POP vein above the knee crease. Take 2 measurements of reflux (Step 9).
14. Move the probe down the leg to the POP vein below the knee crease. Take 2 measurements of reflux (Step 9).

Superficial veins:

The superficial veins will appear much higher on the screen as they are so close to the skin. It is important to hold the probe very lightly when scanning the superficial veins to avoid closing the vein walls. When imaging the GSV and SSV, the image often resembles an eye. If you press the probe lightly, the vein walls should close to make it look as though the eye is winking at you. Also, often when scanning the superficial veins, you may see the deep veins further down the screen. Use the depth button to reduce the depth so that you're imaging the superficial veins only.

15. In transverse, go back to viewing the SFJ.
16. Turn longitudinally and follow the GSV down to just below the junction. Take 2 measurements of reflux (Step 9).
17. Still in longitudinal, follow the GSV down to the lower third of the thigh. Take 2 measurements of reflux (Step 9).
18. Follow the GSV down to the upper calf. Take 2 measurements of reflux (Step 9).
19. Follow the GSV down to the lower calf Note that, as the probe is close to the ankle, you will have to squeeze the foot to initiate blood flow rather than squeezing the calf.

IMPROVING THE PICTURE QUALITY

DEPTH – To get a clear picture, the depth should be reduced when imaging superficial veins and increased when imaging deep veins.

FOCUS – To get the best image, the focus should point towards the vein being scanned.

DOPPLER – Change the brightness according to the deep or superficial veins being scanned.

IF THE PARTICIPANT FEELS UNWELL

If any participant 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 participant is lying flat, offer them a glass of water and do not resume the examination until they feel well enough.

FURTHER SCANNING

Anyone we suspect having a deep vein thrombosis (i.e. 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. Inability to detect flow in the superficial veins does not carry the significance and does not require a return visit for a repeat scan.

APPENDIX 16: REPORT SENT TO PARTICIPANT'S GENERAL PRACTITIONER

Study no:

Date

Dr
Address 1
Address 2
Postcode

Dear Dr

Re: Participant name, address, date of birth

The above patient was seen on ……. as part of the Edinburgh Vein Follow Up Study. I enclose a copy of the 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.

I hope this information may be of help. If you need any more information, please do not hesitate to contact me on 0131 650 3249 or Lindsay.Robertson@ed.ac.uk.

Yours sincerely

Lindsay Robertson

Lindsay Robertson
Research Fellow

EDINBURGH VEIN FOLLOW-UP STUDY

RESULTS OF STUDY EXAMINATION

Study no:

Name:

Address:

Date of birth:

Height:

Weight:

BMI:

CLASSIFICATION OF VENOUS DISEASE

(Grading = Absent / Mild / Moderate / Severe)

	RIGHT	**LEFT**
SPIDER VEINS	mild	mild
RETICULAR VARICES	moderate	absent
TRUNK VARICES	mild	severe
CHRONIC VENOUS INSUFFICIENCY	absent	absent

DUPLEX SCAN – INCOMPETENCE OF VENOUS VALVES

(Grading for incompetence = Absent / Mild / Moderate / Severe)

	RIGHT	**LEFT**
DEEP VEINS	absent	moderate
GREAT SAPHENOUS VEIN	mild	mild
SMALL SAPHENOUS VEIN	absent	absent

COMMENTS .....

APPENDIX 17: KAPPA STATISTIC AND LEVEL OF AGREEMENT

KAPPA SCORES AND LEVEL OF AGREEMENT

KAPPA STATISTIC

Studies that measure agreement between two or more observers should include a test statistic that takes into account the fact that observers will sometimes agree or disagree merely by chance. The kappa statistic (K) assesses the reliability of agreement between observers when assigning categorical ratings to a number of items. The measure calculates the degree of agreement in classification over that which would be expected by chance and is scored as a number between 0 and 1, thus giving a quantitative measure of the magnitude of agreement between observers. To assist in converting the kappa value to a qualitative value of the level of agreement, Altman (1991) provided the following guidance for interpreting the kappa statistic.

Value of K	Strength of agreement
<0.20	Poor
0.21-0.04	Fair
0.41-0.60	Moderate
0.61-0.80	Good
0.81-1.00	Very good

The kappa statistic alone is appropriate if the items in cross tabulation are relatively balanced. However, if the prevalence of a condition is very high or low, the value of kappa may indicate a low level of reliability even when the observed proportion of agreement is high. In these instances the kappa value alone is insufficient. Therefore it is recommended that kappa values should always be reported with level of agreement to provide a clearer picture of agreement between observers (Sim & Wright 2005).

LEVEL OF AGREEMENT

Level of agreement is measured by taking the proportion of participants correctly identified at the same grade of clinical disease between observers or classification method. For example, when comparing two different observers, the proportion of participants correctly identified as having grade 1 varicose veins by observer 1 is compared to those identified as having grade 1 varicose veins by observer 2. The proportion for each grade of disease is measured and then added up to form the level of agreement. In a similar manner, level of agreement can be calculated for the presence or absence of venous reflux determined by two different observers or by one observer on two different ultrasound examinations. When discussing quality control measures in this study the kappa values and level of agreement are reported, where possible. For conditions where the cross tabulation was asymmetrical e.g. one observer found cases of reflux and the other did not, the kappa statistic could not be calculated and therefore only the level of agreement is presented.