Leg ulceration: An exploration of the role of socio-economic factors in the epidemiology, access to health care and outcomes.

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Abstract

Background

Tackling health inequalities has been a priority policy area for the NHS since the 1990's. To date there has been scant research addressing this area in relation to leg ulcers, despite there being some evidence of inequalities in leg ulcer prevalence. The overarching aim of this thesis is to examine the relationship between the epidemiology, management and outcomes of leg ulcers in relation and socio-economic factors.

Methods

The epidemiology and management of leg ulcers was examined using the GPRD and THIN primary care databases. Regression models were undertaken to quantify the relationship between variables and leg ulcer rates. Multilevel logistic models were undertaken to examine three aspects of guideline recommended care in the cohort of patients diagnosed with incident venous leg ulcers; initial assessment using Doppler ultrasound, provision of compression bandaging and referrals. Analysis conducted using the THIN database adjusted for Townsend deprivation fifth rank of each patient, a proxy measure of socio-economic position. Analyses of patient management using the GPRD adjusted for practice level deprivation. Second, the relationship between socio-economic position with leg ulcer outcomes including healing and adverse events was investigated using two recently completed leg ulcer treatment RCTs.

Results

Socio-economic gradients were found in rates of incident venous and prevalent venous and arterial leg ulcers. The reported management of most patients fell short of standards recommended by leg ulcer guidelines although there were wide variations between practices. Only the initial assessment of patients was found to have a relationship with deprivation. Patients living in or attending practices in the most deprived areas had reduced odds of having a record of receiving Doppler assessment of their leg. No relationship was observed between deprivation and healing or adverse outcomes in the clinical trials.

Conclusions

There are health inequalities evident in leg ulcer development and some aspects of management. The wider implementation of guideline recommendations for care may have the potential to ameliorate some of these health inequalities as results demonstrated that low socio-economic position patients were no less likely to achieve positive leg ulcer outcomes when provided with high quality care.

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List of abbreviations

ABPI	Ankle Brachial Pressure Index
AMR	Acceptable Mortality Reporting
CI	Confidence Interval
CREST	Clinical Resource Effectiveness Support Team (Northern Ireland)
EMBASE	Excerpta Medica Database
Exp	Exponential
GP	General Practitioner
GPRD	General Practice Research Database
HES	Hospital Episodes Statistics
MHRA	Medicines and Healthcare products Regulatory Agency
RA	Rheumatoid Arthritis
RCN	Royal College of Nursing
RCT	Randomised controlled Trial
SD	Standard Deviation
SE	Standard Error
SEP	Socio-Economic Position
SIGN	Scottish Intercollegiate Guidelines Network
SSB	Short Stretch Bandage
THIN	The Health Improvement Network
UTS	Up to standard
UK	United Kingdom
4LB	Four Layer Bandage

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Declaration

I declare that the thesis is my own composition and has not been submitted in part or whole for any other degree.

Emily Petherick
September, 2010.

1.0 Introduction

The reduction of health inequalities, defined as '*differences in health that are socially or economically determined*' (Black 1980), is central to current government and National Health Service (NHS) policy (NHS 2007). The role of health inequalities in the epidemiology, outcomes and access to health care for persons with leg ulceration has remained largely unexplored in the United Kingdom (UK).

There is no consensus definition of a leg ulcer. However, one definition that has been widely used is '*tissue breakdown on the leg or the foot due to any cause'* (Cullum 1994). Others have further refined these earlier definition adding '*that a chronic leg ulcer is defined as an open lesion between the knee and ankle joint that remains unhealed for at least four weeks'*(SIGN 1998). Prevalence studies undertaken both in the UK and internationally, suggest that chronic leg ulceration affects up to one percent of the population, however only 20-25% of people have an open ulcer at any time (Graham et al. 2003a). Prevalence of leg ulceration has been shown to be higher in women, although prevalence increases with age for both genders (Margolis et al. 2002).

The management of leg ulcers places a significant economic burden on the NHS. The costs of caring for those with leg ulcers have been previously estimated at between £150–600 million per year (Husband 1996). Up to date figures on the costs of leg ulcer care are not available, however it is likely that costs have increased since this earlier study due to the increasing costs of treatments, such as wound dressings, and staffing in the NHS.

Studies suggest that the majority of leg ulcers are associated with venous disease (estimates range from 40 to 80%), but other risk factors can include immobility, obesity, trauma, arterial disease, vasculitis, diabetes and neoplasia (Cornwall et al. 1986; Moffatt et al. 2004; Simon et al. 2004). Regardless of the pathology, all leg ulcers represent a failure of the underlying vessels to effectively transport blood to and from the lower limbs. Most leg ulcers are slow to heal with up to 68% of cases recurring within a two year period (Finlayson et al. 2009). Leg ulcers typically weep, smell, reduce mobility, and can be incapacitating and socially isolating (Graham et al. 2003b).

There are several reasons why study of the impact of socio-economic factors on leg ulcer disease is needed. It is known that some of the risk factors for leg ulcers, for example obesity, have a social gradient where the prevalence of obesity is higher in low socio-economic status women (Rennie &Jebb 2005). Furthermore, it is known that the risk of both venous insufficiency and peripheral arterial disease are positively associated with cigarette smoking (Gourgou et al. 2002; Willigendael et al. 2004) which itself has a social gradient.

There is some evidence that stress influences wound healing (Kiecolt-Glaser et al. 1995). Furthermore, stress may have psychosocial associations with an individuals' socio-economic status (Chandola et al. 2006). Work undertaken by Chandola et al. (2006) showed that occupational social class was associated with the development of the metabolic syndrome, a clustering of risk factors for the development of cardiovascular disease. There is also evidence that socio-economic factors influence the nature of, and access to the health care that people receive (Husband 1996; Hippisley-Cox et al. 2004). The social determinants of health may therefore influence many aspects of the development of and recurrence of a leg ulcer. Figure 1 below illustrates a conceptual framework to describe the interdependent relationships between the social determinants of health and the biological and psychological factors that contribute to leg ulcer development and prognosis. The model links socio-economic factors to other possible aetiological causes which may underlie both the development and healing of leg ulcers.

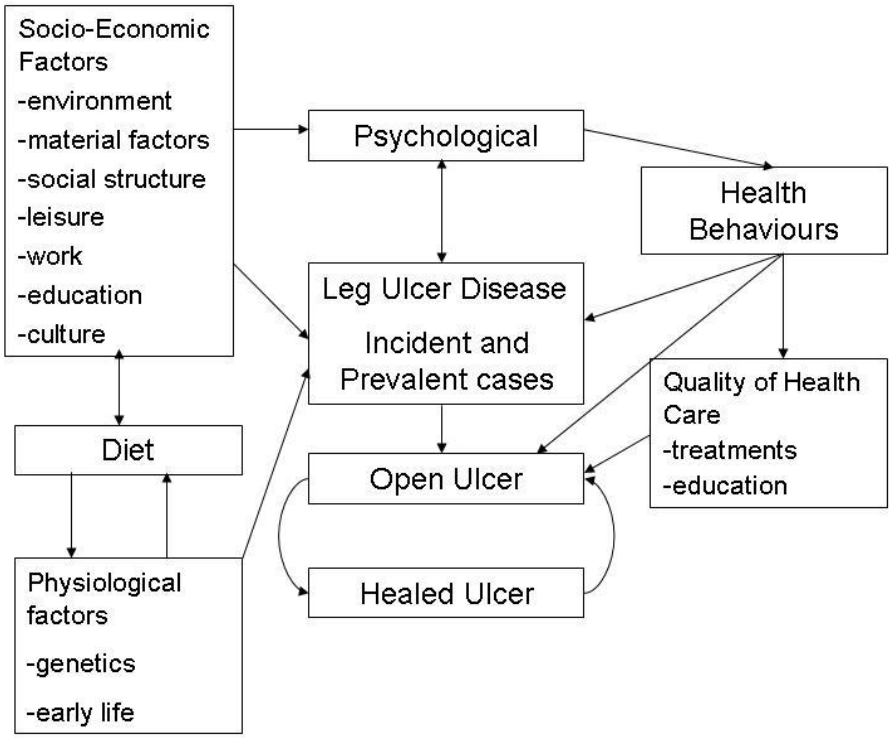

Figure 1 Social determinants of health (developed from Marmot & Wilkinson (2006)

Studies that examined the contribution of socio-economic factors to both the development and management of leg ulceration were sought in order to establish evidence also existed. Only four studies were identified. One study examined the socio-economic distribution of a prevalent population of leg ulcer patients (Callam et al. 1988); one study used a case-control design to examine the likelihood of leg ulcer healing according the socio-economic status of the patient (Franks et al. 1995b); the final two studies examined the association of leg ulceration with social

factors, including both socio-economic status and broader social conditions (Fowkes &Callam 1994; Moffatt et al. 2006).

Callam et al. (1988) and Franks et al. (1995b) concluded that there were no differences in the either the point prevalence or healing of leg ulcers by social class. In contrast Moffatt et al. (2006) and Fowkes & Callam (1994), found differences in the distribution of leg ulceration by social class, with rates increasing in lower social classes. The results of studies exploring health inequalities in leg ulceration did not produce consistent findings, containing heterogeneous patient populations, methods and measures of social class. A full description of these studies is provided in the literature review, which is presented in the next chapter.

Two studies were located that examined the financial impact of leg ulceration on the individual (Callam et al. 1988; Phillips et al. 1994), and in both cases found negative effects. Callam et al. (1988), found that 21% of patients of working age with leg ulceration had severe work limitations or were unable to work. Philips et al. (1994) found that leg ulceration was positively associated with time lost from work, job loss and adverse effects on finances.

Whilst no study has yet examined the quality of leg ulcer care and socio-economic factors, it is possible that quality of care will be lower in more deprived populations where general practices tend to be smaller (Mackay et al. 2005) and consultation times shorter (Stirling et al. 2001). Similarly Hirst (1998) found that there were lower numbers of practice nurses in areas of above average deprivation. Finally Mackay (2005) observed that practices serving more affluent areas were twice as likely to participate in quality schemes, health service initiatives and postgraduate training compared with those practices located in more deprived areas. It is likely that most, if not all of these factors, previously identified by earlier studies will be associated with care provision for leg ulcer patients.

What makes the monitoring of both health service use and health inequalities in patients with leg ulceration particularly difficult is the lack of routine data collection for this condition. As discussed in parliament (House of Commons Hansard 2006), current data on the numbers of persons treated, costs of care, and locations of specialist leg ulcer treatment centres is not collected by central government within the United Kingdom. Nor is any data collected on the prevalence or incidence of leg ulceration in any of the major surveys of health undertaken, for example by the Health Survey for England, or by any of the longitudinal studies conducted in the United Kingdom, such as the English Longitudinal Study of Ageing.

The majority of prevalence studies of leg ulceration have focussed on small geographic areas using surveys of health professionals to identify patients with leg ulcers. A systematic review of leg ulcer prevalence studies concluded that studies were disparate with respect to populations studied,

definitions of leg ulceration used, case finding methodologies employed, study designs used and methods of assessment and validation (Graham et al. 2003a). Results from the systematic review provided estimates of leg ulcer prevalence that ranged from 0.12 to 1.1% of the population for open ulcers to 1.8% if both open and healed ulcers were used in the estimate (Graham et al. 2003a).

The largest single study of incidence and prevalence of leg ulceration (Margolis et al. 2002) was published after the literature search for the systematic review completed by Graham et al. (2003a). The study undertaken by Margolis et al. (2002) used the UK General Practice Research Database (GPRD) to examine the incidence and prevalence of venous leg ulceration in patients aged 65 years and over. This study found that a large numbers of patients with leg ulcers were being managed in general practice. In addition Margolis et al. (2002) validated the GPRD coding for the diagnosis of venous leg ulceration by obtaining the original records for a sample of patients confirming the agreement between the GPRD coding and the patient records. This validation study estimated that both the sensitivity and specificity of a database diagnosis of venous leg ulceration was greater than 93%. Using the GPRD, Margolis and colleagues found annual prevalence rates of venous leg ulcers in patients aged over 65 years to be 1.69% and incidence rates ranging from 0.76 for men to 1.42 per 100 person years for women (Margolis et al. 2002). These estimates were consistent with previously conducted research (Graham et al. 2003a).

The study by Margolis was the only study of leg ulcer incidence conducted in the UK identified. However, more could be done using the GPRD to examine this topic; Margolis et al. (2002) only studied patients with a READ/OXMIS code indicative of venous leg ulceration and did not examine other forms of leg ulceration or describe the management of these patients. Secondly, the work conducted by Margolis et al. (2002) used data that is at least 10 years old, having been collected between 1988 and 1996 and now requires updating.

Subsequent to the conduct of these studies, the management of leg ulceration has been revolutionised in two main ways. First, clinical guidelines for the management of leg ulceration were introduced (RCN 2006) which may have contributed to a reduction in the prevalence of leg ulceration in the UK. Second, the role of non-medical prescribing has greatly expanded in this time, the number of nurse prescribers now comprising over 11,000 (Association of Nurse Prescribers 2009). Using the GPRD it has been shown that practice nurses now comprise one of the largest groups of non medical prescribing personnel, prescribing at higher rates, than other nurses or midwives (GPRD 2006). Hickie et al. (1998) found that practice nurses saw a greater proportion of leg ulcer patients than general practitioners.

Despite work conducted showing that large numbers of patients sought treatment for leg ulceration in general practice, relatively few studies have examined their management and treatment in general

practice in the UK. Diagnostic and treatment patterns of leg ulcer patients, as well as prescribing and referral patterns within general practice all deserve scrutiny.

There are further options for the expansion of exploration of primary care data. Since the earlier work by Margolis, the availability of primary care data has greatly increased, there now being available a further two primary care databases available for researchers to use which also contain socio-economic data at the patient level. These two databases are the QResearch database and The Health Improvement Network (THIN) database (QResearch 2009; THIN 2009). The use of other sources of primary care data enables the role of socio-economic factors in both the development and management of leg ulceration to be explored. Further discussion of these databases and the socio-economic data they contain will be undertaken later in the thesis.

There are methodological challenges inherent in assessing the relationship between socio-economic position and outcomes. First, it is quite likely that valid outcome data (such as the healing rates and time to healing) will not be present in primary care databases. Once management of the patient has been taken over by other clinical staff outside of the practice, for example community nurses, leg ulcer healing data are often not fed back to general practice. Even where patients continue to be treated by practitioners within general practice healing outcomes are unlikely to be recorded as patients may cease consulting once healing has been achieved.

For these reasons it is probably necessary to explore leg ulcer outcomes using clinical trial data. Whilst acknowledging that participants in clinical trials may not represent the UK leg ulcer population as a whole the proposed analysis will provide a useful starting point for the exploration of the relationship between socioeconomic variables, ulcer healing and adverse events. Second, this analysis will allow comparisons of the representativeness of the socio-economic position of trial participants to the general leg ulcer population. Finally, this analysis will enable valuable exploration of the representativeness of leg ulcer trial populations to be undertaken. Data will be obtained from two recently completed trials of wound care treatments conducted by staff within the Department of Health Sciences, University of York.

This thesis aims to contribute to a greater understanding of the factors that influence the development, management and healing of leg ulcers. This thesis will also explore whether there are inequalities in service provision and inclusion in research associated with patients' socio-economic position. The three overarching aims of the thesis are described below.

Aims of the Thesis:

- To examine the influence of socio-economic position on the incidence and prevalence of leg ulceration.

- To examine the diagnostic assessment, treatment and referral patterns of patients presenting to general practice with leg ulcers and to explore potential differences by patient factors (age, sex, socio-economic position) and by practitioner related factors (practice list size and practice level deprivation).
- To explore the impact of socio-economic position upon healing and likelihood of adverse events and to describe the socio-economic position of leg ulcer trial participants.

2.0 Overview of the literature

The aim of this chapter is to place the objectives of the thesis in the context of the current literature. The present chapter comprises three sections. The first section will provide a general contextual background of leg ulcers including a critical review of the literature that has covered the following areas;

- Leg ulcer pathology
- Studies examining the incidence and prevalence of leg ulceration
- The current evidence base for the treatment of leg ulceration
- The current management of leg ulceration

The second section will provide an overview of the key concept of health inequalities and explains why their reduction is a key component of current NHS policy.

The third and final section will provide a critical review of studies that have examined health inequalities in leg ulcer patients. Current theories of health inequalities will be discussed to provide a contextual basis to the results reported in the studies of leg ulcer inequalities.

2.1 The descriptive epidemiology and management of leg ulceration

The aim of this section is to provide an introduction to studies that have described the epidemiology of leg ulceration. This specifically includes studies that describe the pathology and the population health burden of the condition, focusing on studies that were conducted in the UK. Studies that have explored the management of the condition in primary care are also discussed, as well as guidelines for the care of leg ulceration focussing on both studies and guidelines produced in the UK.

Leg ulceration is not a disease in itself but a manifestation of an underlying disease. Most commonly, the conditions thought to contribute to the aetiology of leg ulcers are venous and peripheral arterial diseases. The descriptive pathology of leg ulceration refers to the disease process that produces a leg ulcer. The aetiology of leg ulcers can be determined, but rarely is. Nelzen et al. (1994) demonstrated that reliance on clinical signs and symptoms alone to diagnose venous disease, without the support of non-invasive diagnostic assessment using Doppler ultrasound to calculate the ankle brachial pressure index, will result in the misclassification of the pathology underlying one out of every four leg ulcers. The extent to which the underlying pathologies are causal for any particular ulcer is unclear, since venous and peripheral arterial disease are both highly prevalent in the elderly population (Fowkes et al. 1991; Robertson et al. 2008).

Leg ulcers typically weep, smell, reduce mobility and can be incapacitating and socially isolating (Graham et al. 2003b). Regardless of the underlying pathology, all leg ulcers represent a failure of the underlying vessels to effectively transport blood to and/or from the lower limbs.

2.1.1 Relative burden of different pathologies of leg ulceration

Studies of the incidence and prevalence of leg ulceration were sought to determine the frequency with which different aetiologies of leg ulcers were observed in population based studies. Studies were included if they examined the incidence or prevalence of various aetiologies of leg ulceration. None of the incidence studies classified ulcers by aetiology; those that mentioned the aetiology of leg ulceration were restricted to ulcers of a single aetiology (i.e. venous ulceration). Of the prevalence studies, only n=8 (25.5%) provided any assessment of underlying ulcer pathology, whereas none of the five incidence studies met the inclusion criteria. The results of the estimates of proportions of ulcer pathologies identified by these studies can be seen below in Table 2.1. A full description of rarer ulcer pathologies can be found in Appendix C.

Table 2.1 Distribution of ulcer pathology within prevalence studies

Author, Year, Country	Study design	Diagnostic method	Venous	Arterial	Mixed venous-arterial	Diabetic	Rheumatic	Other (specify)	Unknown
Cornwall et al., 1986 England	Sub-study of random sample of 100 (31%) of patients identified in a prevalence study.	Photo-plethysmography (PPG) assessment	81%	31%	22%	NR	NR	NR	Note: unclear how these figures derived
Callam et al., 1988 Scotland	Subgroup of patients from point prevalence study (Callam et al., 1985)	Clinical assessment stated, unclear if any device based testing used.	76%	22%	0	0	9%	0	0
Lindholm et al., 1992 Sweden	Leg ulcer patients from prevalence study N=140	Unclear	44%	8%	12%	0	0	21% not stated	15% no response
Dealey 1999 England	Point prevalence Hospital Inpatients N=17	Unclear	29.5%	17.6%	11.8%	0.6%	0.6%	0	29.5%

Table 2.1 Distribution of ulcer pathology within prevalence studies (continued)

Author, Year, Country	Study design	Diagnostic method	Venous	Arterial	Mixed venous-arterial	Diabetic	Rheumatic	Other (specify)	Unknown
Moffatt et al. 2004 England	Point prevalence study N=113 patients with 138 ulcerated limbs Results are presented for limbs	Clinical assessment stated, method unclear	43%	15.2%	20%	1%	0	Arterial and diabetes 1%	Pressure (bandage induced) trauma 2% Multi-factorial (combination) 35%
Pina et al. 2005 Portugal	Point prevalence study N=171	67% clinical opinion 12% ABPI 21% unclear	52%	3%	0	0	0	Mixed not specified 10%	35%
Clarke-Moloney et al. 2006 Ireland	Point prevalence N=449 leg ulcers in 429 patients % per leg ulcer	Doppler measurement of ABPI 71.8% Remainder unclear	63.3%	8%	4%	5.8%	0.4%	Malignancy 0.7% Traumatic 1% Burn 0.2% Pressure 0.2% Scleroderma 0.2%	16.2%

Table 2.1 Distribution of ulcer pathology within prevalence studies (continued)

Author, Year, Country	Study design	Diagnostic method	Venous	Arterial	Mixed venous-arterial	Diabetic	Rheumatic	Other (specify)	Unknown
Vowden & Vowden 2009 United Kingdom	Point prevalence N= 482	NR	40.5%	13.5%	11.4%	14.1%		6.2% Not specified	14.3%

NR-Not reported

The most frequently described pathology associated with leg ulceration was venous disease. Other common pathologies reported included arterial disease, diabetes and rheumatoid arthritis. Frequently more than one potential pathological factor was identified and in most studies there were a proportion of patients for whom the underlying pathology was not able to be determined.

In the prevalence studies located two main methods of diagnosing the pathology of leg ulcers were reported: clinical opinion and ruling out the existence of certain pathologies using device based testing. The use of clinical opinion relies upon differential diagnosis, i.e. determining the underlying cause of leg ulceration based upon available signs and symptoms. Device based testing using Doppler ultrasound provides another useful adjunct method to determine the underlying pathology of the leg ulcer by assessing the circulation in the leg. This information can then be used in conjunction with the clinical signs and symptoms identified to provide a more comprehensive diagnostic picture.

Comparison of the results of the prevalence studies was difficult due to differences in the methods used to determine the underlying pathology of leg ulceration. Additionally, in all of the studies identified underlying leg ulcer pathology had been collected as part of cross sectional point prevalence studies. Therefore any differences in the frequencies of different leg ulcer pathologies observed between studies could be due to differences in the populations studied, time periods over which they were studied or due to diagnostic and/or methodological differences.

2.1.2 Population health burden of leg ulceration

To explore the population health burden of leg ulceration, studies of the incidence and prevalence of any forms of leg ulceration were sought. No restrictions were applied regarding the definition of leg ulceration used or to the country where the study was conducted. The only studies excluded were those that examined the prevalence of all wound types, but did not provide the data for leg ulcers separately and to non-English language publications. A systematic review of prevalence studies was located (Graham et al. 2003a) which had a search date of 1966-2000. Due to the comprehensiveness of this systematic review a further search for studies was made from the year 2000 to July 2010 only. Two of the earlier prevalence studies, Callam et al. (1985) and Callam et al. (1988) were re-examined in detail as they were two of the largest studies undertaken in the UK that had examined both the prevalence and pathology of leg ulcers. In addition, the study by Callam et al. (Callam et al. 1985; 1988) was the first study conducted in the UK to evaluate the influence of socio-economic position on the prevalence and duration of leg ulceration.

This section will begin by providing an overview of leg ulcer prevalence studies and will conclude with a discussion of incidence studies. Searching forward from the year 2000, a total of 8 reports of 7 studies were found, 2 of which were undertaken in the UK. For completeness a summary of all prevalence studies included in the systematic review (Graham et al. 2003a) and those located subsequently is provided in Appendix A. With the exception of the Margolis et al. (2002) study which used national data, the remaining studies restricted their examination to the prevalence of leg ulcers in specific geographical regions within countries.

The study by Callam et al. (1985) examined a larger sample of leg ulcer patients (n=1477) than any previous UK based prevalence study. Practitioners within primary care (general practice, community nursing and occupational health services) and secondary care (physiotherapy departments, outpatient departments, hospital inpatients and old people's homes) were surveyed. Health professionals were asked to provide study investigators with details of patients that they were currently treating or had treated for leg ulcers in the preceding three months (in the time period 1981-2), within the health board areas of Lothian and the Forth Valley. Responses were received from 93.5% of practitioners approached. The accuracy and completeness of the responses from the health care providers was not assessed. The majority of patients (87%) were found to be managed in the community, by community nursing services and general practitioners. Callam et al. (1985) estimated an overall point prevalence of 1.48 per 1000 population, with prevalence observed to be higher in women of all ages, and with increasing age for both sexes. The authors of this study did not specify whether the denominator used was the total or the adult population.

Following up their earlier prevalence study, Callam et al. (1988) then undertook a sub-study which comprised a clinical assessment of 600 of the 1477 leg ulcer patients previously identified (Callam et al. 1985). There were two inclusion criteria used for this study: first that the patients' general practitioner was willing to provide consent for researchers to contact their patient, and second the patient provided consent and could be clinically assessed within the time limits of the study (Callam et al. 1987). The clinical assessments were undertaken by a single clinician and consisted of a detailed history, examination and any other relevant investigations. The nature of these other investigations and the rationale for implementing these was not described. The underlying pathology of patients' leg ulcers was investigated, and 76% of ulcers were found to be associated with venous disease, 22% with arterial disease and 9% with rheumatoid arthritis. Until the age of 40 both sexes were observed to have a similar prevalence of leg ulceration. From the age of 40 the prevalence of leg ulceration increased in females compared to males. Incidence estimates were obtained by self report from patients. Most patients reported they developed a leg ulcer aged 50 years or greater (60%). However, 22% of patients reported that they first developed

a leg ulcer before the age of 40 and 40% before they were 50. The age at which males and females first developed a leg ulcer followed a similar pattern to prevalence, with males and females having a similar distribution of onset until the age of 30. After this age, more women than men developed leg ulceration. It is unclear what degree of recall error may have been present given the lengthy duration of leg ulceration experienced by this patient group.

Graham et al. (2003a) undertook a systematic review of prevalence studies of lower limb ulceration, searching from the year 1966 to 2000 and finding 22 studies, including the Callam et al. (1985) study described above. Estimates of prevalence in the included studies ranged from 0.12% to 1.1% of the population for open ulcers to 1.8% if both open and healed ulcers were used in the estimate (Graham et al. 2003a). Studies were found to be disparate with respect to populations studied, definitions of leg ulceration used, case finding methodologies employed, study designs used and methods of assessment and validation(Graham et al. 2003a). The epidemiological methods used will have a direct bearing on the estimates produced, with point prevalence estimates, that being estimates of disease prevalence at a particular point in time (e.g. a day or month) producing smaller results on average than results of period prevalence, where the estimates are based on observation of cases occurring over a longer duration. Given the heterogeneous nature of the studies included in the systematic review, no attempt was made to pool the results of these studies. Where studies examined variations is rates by the age and sex of participants, prevalence was generally higher in women than men, although increases with age were observed for both genders.

A further nine reports of eight studies have been published since 2000, three of which were conducted in the UK. These studies had prevalence results that fell within the estimates, and were subject to the same methodological disparities including inclusion of different populations and using different case finding methodologies as were observed previously described in the systematic review of prevalence studies conducted by Graham et al. (2003a). The four most recent prevalence studies conducted using data from the UK and Ireland are discussed in detail below.

One of the four recent UK studies used the General Practice Research Database (GPRD) to describe the prevalence of venous ulceration in people aged 65 years and over consulting in general practice (Margolis et al. 2002). The GPRD contains data collected from over 3 million active patients within general practice, constituting about 6% of the UK population (Margolis et al. 2002). Patients were eligible for inclusion in the prevalence study if they were 65 years or greater at the time of the study, had made at least one visit to the GP practice within a given year, and had a Read code recorded in their database record that was indicative of a clinic visit for

venous ulceration. Database records of patients with leg ulcers were selected from 1988 to 1996 inclusively, consisting of a 10% random sample of the full GPRD elderly population over this time period. This same patient group was used to calculate both the numerator and denominator of the study. To ensure that database records were sufficiently accurate, a sample of records, which were coded both positive and negative for leg ulcers from the database were validated against the original medical records. The database diagnosis was found to be highly sensitive and specific (sensitivity 93.4%, specificity 98.1%). Average annual prevalence rates of 1.69% (95 % CI: 1.65 -1.74) were found for the elderly population with venous leg ulceration consulting in general practice over the time period 1988 to 1996. Further stratification of rates, such as age or sex specific prevalence rates, were not reported.

The second recent UK study, conducted by Moffatt et al. (2004), examined the prevalence of chronic leg ulceration in a single health district of London. Patients were identified by surveying health professionals (including nurses, general practitioners, hospital wards and specialist out-patient services) within one district of London. The denominator for this study was described as the total population of the Wandsworth area of London. Health professionals were asked to provide details of any patients who were suffering from a leg ulcer over the previous four week period in 1998 (Franks, personal communication 2006). Like the earlier prevalence study undertaken by Callam et al. (1985), no validation of the responses received were undertaken. Patients who provided informed consent were then invited to partake in a clinical assessment comprising of medical history (including recording the size and duration of ulceration) and assessment of risk factors for ulceration by research nurses. Although the authors mentioned using non-invasive vascular investigations it is unclear whether all patients underwent a standardised diagnostic assessment. It is unclear what proportion of patients consented to take part in the study and whether there were any differences between the patients who consented to take part compared to those that declined.

Moffatt et al. (2004) found crude prevalence estimates of 0.45 per 1000 people (95% CI 0.37-0.54/1000). For men the rate was 0.34 per 1000 people and for women 0.5 per 1000 people. Rates increased greatly with age, men aged greater than 85 years had prevalence rates of 8.29 per 1000 people and for women 8.06 per 1000 people. It is unclear how representative the patient group within this study was of those commonly encountered in the community, as over 70% of the patients identified in this study had been referred to hospital for specialist leg ulcer advice. This may not constitute usual care for large proportions of leg ulcer patients within the UK.

It is further noted that the prevalence estimates reported by Moffatt et al. (2004) are lower than other published estimates which ranged from 0.21% to 1.8% (Graham et al. 2003a). The authors

reported that the denominator used was the population in the Wandsworth area of London (population 252,000) although it was unclear whether this was the adult or total population in the area. A search of the 2001 census indicated that Wandsworth had a population of approximately 260,000 at this time, this was three years after the study by Moffatt et al. (2004). It would therefore appear that the denominator used in the study was the total, rather than the adult population, thus explaining the lower estimates of prevalence obtained compared to other published studies.

Next, McDermott-Scales et al. (2009) conducted a point prevalence study in a district of Ireland. Case ascertainment for this study consisted of inviting nurses working across a wide range of areas including: intellectual disability, psychiatry, general practice, nursing homes and addiction services, amongst others, to perform a survey of all wound patients that they were currently treating. All nurses were provided with an education session to learn how to use the data collection tool for this study. The point prevalence of leg ulcers was 2.9%. This figure must however be interpreted with caution as the denominator used was the number of patients seen by all nurses on this date. Unlike the other studies examined thus far, the results from this study are not population estimates using registered patient populations or census population estimates, but rather a one day treated population estimate. Furthermore, unlike some of the other studies nurses were only asked to report on the number of patients that they were treating on the day of the study rather than the number of wound patients that were currently registered within their healthcare setting. Although the study also reported the prevalence of all wounds using the total population as the denominator, separate prevalence results were not provided for leg ulcer patients, so their prevalence in the community remains unknown. This was the only study to report results in this manner making the external generalisability of this study low as the methodology used is likely to overestimate leg ulcer prevalence relative to other studies that have used population based denominators.

Finally, a point prevalence study of all wound types was conducted within a single health region, using data from primary, secondary and nursing home care in the north of England (Vowden &Vowden 2009). This study used a survey questionnaire design to determine the point prevalence of all forms of wounds in primary care trusts, acute care settings and nursing homes during a single week in March 2007. In primary care trusts a community nursing team leader was responsible for ensuring that all patients with wounds had their data recorded by practice nurses. In nursing homes and acute care settings data collectors visited to abstract the information using a standardised survey collection tool. It was unclear if any further validation of the case ascertainment strategy was performed. The reported crude prevalence of leg ulcers of any form

was 0.98 per 1,000 population and 0.39 per 1,000 population with venous leg ulcers. In this study the denominator used was the total population in the area.

Incidence

Only five incidence studies were found. Of these studies, one was undertaken in the UK, two were conducted in America and two were conducted in New Zealand using a single data source explored using two different methodological approaches. As only a small number of incidence studies were located they are all described in full.

The earliest leg ulcer incidence study identified was a retrospective cohort study by Wipke-Tevis et al. (2000) who used a minimum data set from an aged care facility in Missouri to locate patients. They identified patients who were leg ulcer free upon arrival and subsequently developed venous leg ulcers within the first 90, 180, 270 and 365 days of moving to the facility. The type of incidence calculated was cumulative incidence and the denominator was the number of persons admitted during the same respective time periods who did not have a leg ulcer at the time of admission. Cumulative incidence rates at 90, 180, 270 and 365 days after admission were 1.0%, 1.3%, 1.8% and 2.2% respectively. The high rates observed in this study are likely related to the older age of the sample whose age averaged 81 years. The authors did not state if they examined any historical records of these patients. There is therefore the possibility that some of the venous leg ulcers these patients developed upon entry to the nursing home were recurrences of previous venous leg ulcers, and not incident cases per se. Additionally, these patients are by definition the frail elderly population who are likelier to have many co-morbidities which may predispose them to the development of leg ulcers.

The lowest estimates of incidence came from Heit et al. (2001), who conducted a study in Minnesota, United States of America, examining the incidence of venous leg ulcers within a single county over a time period of 25 years. The county examined had a centralised collection of clinical records from primary, secondary and nursing home care. The study employed a retrospective cohort study design to search for patient records with a first occurrence of a venous leg ulcer in persons aged 15 years or greater throughout the study period of January 1966 to December 1990. Once the records were identified, experienced nurse abstractors then reviewed the complete in and outpatient records for all patients identified as potentially eligible and abstracted demographic details. These included age at incident event, sex and year of diagnosis. The denominators used for this study were the age sex specific estimates of the population from census data for 1960, 1970, 1980 and 1990 with linear modelling techniques used to provide estimates for the between census years (Bergstralh et al. 1992). The method of incidence calculation was incidence density. This method of incidence calculation was the ideal method to

use in this study population as it accounts for the open nature of the cohort being examined. Total results were directly age and sex standardised to the 1980 United States Population.

Heit et al. (2001) found age, sex standardised average annual estimates of 18 per 100,000 person years for venous leg ulcer incidence over the entire study period of 1966 to 1990. Rates stratified by age and sex were shown to vary from 1.5 in women aged 15 to 34 to 134.7 per 100,000 person years in women aged greater than 85. Rates for men varied from 2.2 for men aged 15-34 to 96.7 per 100,000 person years in men aged 85 years and greater. Venous ulcer incidence rates were shown to be higher in females compared to males, and increased with age in both genders. Rates of incident venous leg ulceration were shown to decrease, although they were found to be relatively stable from 1980 to the end of the study period in 1990. This was the only study of incidence identified that explored differences in incidence rates over time. As the authors performed direct standardisation the results obtained were not biased by changes in population demographics (i.e. rates are not only changing due to increasing numbers of elderly in the population over time).

Walker et al. (2002a) conducted a cumulative incidence study in New Zealand. Case ascertainment of leg ulcer patients consisted of surveying health professionals to provide details of patients that they were currently treating or had treated and self-notification from patient's themselves so that patients who self treated could be identified. Regardless of the case ascertainment strategy used, all patients were identified over a one year period from the 1st November 1997 to 31st October 1998. The response rates from the surveys of health professionals were not reported. In this study a broad definition of leg ulcer was used with leg ulcers defined as any breaks on the skin on the lower leg or foot which had been present for more than six weeks. The authors did not provide any further detail indicating how incident cases were defined. Observed estimates of annual cumulative incidence rate were 32 per 100,000 population. The denominator used in this analysis was the total population (personal communication N. Walker) of North and Central Auckland rather than the adult population, which would explain the lower rate observed in the results by Walker et al. (2002a).

A further incidence study was conducted in New Zealand using capture-recapture analysis which produced incidence estimates of 252 per 100,000 people (Walker et al. 2002b) using data obtained from the earlier study by Walker et al.(2002a). The capture- recapture method was originally developed by ecologists to estimate wild animal populations. The method was used by Walker et al. (2002b) to estimate the number of unidentified leg ulcer cases in addition to the identified cases. The name capture recapture comes from studies where animals were captured, tagged and released, then recaptured in an attempt to estimate the number of animals in a

particular area (Seber 1982). Capture-recapture analysis provides an estimate of the population hypothesised to have leg ulcers based on the assumption that both capture and recapture are independent and that the population is closed. In the case of the study by Walker et al. (2002b) this first assumption would be that the chance of being identified either by a health professional or being self notified are independent and have the same probability of occurring (Seber 1982). Using capture-recapture the number of leg ulcer patients hypothesised to be living in the community was 252 cases per 100,000 per year (95% C.I. 138-566).

There were several methodological limitations to the study conducted by Walker et al. (2002b). First the two assumptions of the capture recapture study design were not met. Leg ulcer patients may not have had the same probability of being captured using the two methods of case ascertainment, as patients have different access to medical care. Second, the assumption of a closed population was not met as patients may have entered and left the area during the year study duration. Furthermore, no independent verification of any of the identified cases were performed. Hence, it remains unclear as to whether or not the larger rates observed in this study may have been biased due to misclassification of ulcer status rather than the methods employed by this study. Moreover, the misclassification encountered in this study is likely to be differential as both the leg ulcer diagnoses of health professionals and patients were treated equally, whereas they are more likely to be heterogeneous as there will be a certain proportion of patients who chose to self-treat rather than seek health professional intervention. Interestingly the results of this study also indicated that health professionals underreport leg ulcer cases. This result is to be expected considering the design of the health professional survey used which was heavily reliant upon the accuracy and enthusiasm of the health professionals providing data.

The final study identified was conducted by Margolis et al. (2002) using UK primary care data from the GPRD to estimate the incidence density of venous leg ulcers in the registered general practice population aged 65 years to 95 years. The methods of case ascertainment and case validation used in this study were described in full in the prevalence section so are not repeated here. Two additional inclusion criteria were applied to ensure that only incident cases were identified Margolis et al. (2002). First, that all incident cases had no other form of leg ulcer was diagnosed in the 3 months post incident venous leg ulcer diagnosis and that the incident diagnosis came at least six months after first registration with the general practice. Overall crude incidence rates observed for average annual incidence rates over the entire study period were 0.76 per 100 person years for men and 1.42 per 100 person years for women. These results were the highest rates of leg ulceration reported in any of the leg ulcer epidemiology studies identified. Although these results would be expected to be high as they are from an older population than other studies, the magnitude of difference was very large indeed. As an example, the crude rate of

venous leg ulcers in women aged 85 years or more reported by Heit et al. (2001) was 134.7 per 100,000 person years, the rate reported by Margolis et al. (2002) for women aged 86 to 90 years was substantially higher at 2,300 per 100,000 person years. The reason for the difference in rates between the results of these two studies is unclear, but may indicate substantial differences in the populations sampled and the case ascertainment strategies used.

The results of the incidence studies mirrored the earlier results of prevalence studies, with women generally observed to have higher rates of incident leg ulcers than men across most age groups, and incidence rates increasing with age for both genders. In common with the prevalence studies, incidence studies showed a large variation in the definitions of leg ulcers used, the population included, the methods employed to find cases and methods of data analysis. Three studies searched medical or administrative database records to find cases (Wipke-Tevis et al. 2000; Heit et al. 2001; Margolis et al. 2002) whilst in the remainder of studies incident cases were identified by surveying health professionals and two studies also additionally recruited patients directly via the media (Walker et al. 2002a; Walker et al. 2002b).

Summary of incidence and prevalence studies

To summarise, there have been several methodological problems with the majority of prevalence studies undertaken to date. Many (Callam et al. 1985; Graham et al. 2003a; Moffatt et al. 2004; McDermott-Scales et al. 2009) have relied on surveys of healthcare providers to identify cases but then failed to report the response rates or undertake validation of survey responses. Only three studies conducted a validation of the case ascertainment strategy (Heit et al. 2001; Margolis et al. 2002; Vowden &Vowden 2009). Margolis et al. (2002) checked a random sample of records to ensure that the database record of leg ulceration was consistent with the patient's written records, and good rates of sensitivity and specificity achieved. Heit et al. (2001) and Vowden & Vowden (2009) used trained abstractors to check potentially eligible cases against details in clinical records to achieve accurate diagnoses.

Although there have been some good quality studies, no recent studies have reported on the contemporary distribution of leg ulceration in the general adult population of the UK. Over the past decade, treatment options and practitioners knowledge are likely to have increased, and evidence based practice, such as that based on the RCN guidelines (RCN 2006) first introduced in 1996, has arguably become more widespread. Additionally, the proportion of the population aged 65 years and over has continued to rise in this time period, creating a greater pool of the population at risk of developing leg ulcers, and as people are living longer they are likely to have longer leg ulcer duration if they do develop the condition (Office of Health Economics 2007).

Only two studies have yet examined the relationship of socio-economic position to the distribution of leg ulceration within a population (Callam et al. 1988; Moffatt et al. 2004). In general results suggest it is difficult to recruit lower socio-economic status patients to research studies (Burroughs et al. 2003; Fouad et al. 2004), so it may be that the poorest subgroups of patients have not been successfully recruited to these studies biasing the observed results.

Comparisons between incidence and prevalence studies are further hampered as the vast majority of studies present non-standardised estimates. Although results from these studies appear similar, comparison of non-standardised results may mask significant differences in the estimates obtained from studies if there are differences in the age structures of the populations compared.

2.1.3 Organisation of leg ulcer care in the UK

The majority of leg ulcer patients are treated entirely in the community by primary care practitioners (Community nurses, Practice nurses and General Practitioners). Accurate, up to date figures on the frequency and proportions of leg ulcers treated are hampered by lack of systematic and centralized data collection within primary care, particularly for community nursing activities. Unlike care provided within hospital, for which Hospital Episode Statistics (HES) are available, no equivalent exists for the provision of care within primary care; irrespective of who provides the care.

There are a number of difficulties in accessing leg ulcer management data from the full range of practitioners who provide leg ulcer care although there are different issues for different practitioner groups. Difficulties with obtaining community nursing data include the fact that patient records are often held by the patients themselves to facilitate information sharing between visiting practitioners (Owen 2005) and are logistically difficult to obtain. For general practice data there is no central collection of activities undertaken within primary care by general practitioners and practice nurses, except for those activities which are part of the Quality of Outcomes Framework (QOF). For all providers, the availability of electronic records, particularly outside of general practice, which allows the sharing of information between different primary care providers, such as community nurses and general practice, is very much in its infancy, still being trialled and only available from particular software providers (E-Health Newsletter 2006). Recent figures suggest that up to 95% of all general practices now use computers to both store and access patient data (Dobrev et al. 2008). Similar figures do not exist for community nursing teams but due to the mobile nature of their practice it is unlikely that rates of electronic data collection are as high as in general practice.

2.1.4 UK Standards of leg ulcer care

Three different clinical guidelines for the care of leg ulcers have been produced (CREST 1998; SIGN 1998; RCN 2006) providing recommendations for the diagnosis and management that should be provided to leg ulcer patients. The conclusions of the guidelines are summarised below in Table 2.2.

Table 2.2 Summary of UK clinical guidelines for the assessment and management of leg ulcers

Clinical assessment	History and clinical examination of the leg ulcer noting appearance and presence of other conditions (e.g. diabetes and rheumatoid arthritis) that may exacerbate the leg ulcer.
Device based testing	Measure ankle-brachial index (ABPI) by hand-held Doppler ultrasound to guide diagnosis. Patients with ABPI >0.8 assumed to have venous origin to ulceration Patients with ABPI <0.8 assumed to have arterial disease Clinical history needs to be taken to exclude other possible diseases.
Management	Venous ulcer: patients with venous ulcer to treated with graduated multi-layer compression bandaging Non-venous ulcer: patients should be referred to an appropriate specialist.

Adapted from CREST (1998), SIGN (1998) and RCN (2006).

The three UK clinical practice guidelines for leg ulceration all concluded that patients presenting with an ulcer should be screened for the presence of peripheral arterial disease by Doppler ultrasound-assisted measurement of ankle brachial pressure index to ensure detection of arterial insufficiency (CREST 1998; SIGN 1998; RCN 2006). An exploration of studies examining the diagnostic management of leg ulcer patients has found that this assessment approach is often not implemented in routine clinical practice. Hickie et al. (1998) conducted a study of leg ulcer management in primary care undertaken in Scotland and found that only 8% of health professionals (including general practitioners, practice nurses and community nurses) undertook assessment of their patients using Doppler ultrasound assisted measurement. Two studies were found that examined the diagnostic methods used by community nurses. Stevens et al. (1997) found that over 80% of leg ulcer patients known to a community nursing service had not been assessed using Doppler ultrasound, whilst Elliot et al. (1996) found that 50% of professionals used visual assessment alone to determine ulcer type. Graham et al. (2003b) surveyed the knowledge of primary care physicians in Canada and found that only 16% of respondents reported confidence in their ability to manage leg ulcers. Sadler et al. (2006) conducted a similar study in Australia and found that general practitioners were largely confident in their knowledge

of leg ulcer management. Despite this confidence, the general practitioners surveyed by Sadler et al. (2006) were found to rarely adhere to guideline recommendations for the management of leg ulceration.

The assessment and provision of services to leg ulcer patients is undertaken by a wide range of health professionals, but there are few data to show how leg ulcer care is delegated and managed. A survey of the management of leg ulcers in primary care settings in Scotland found that the initial assessment of the person with a leg ulcer was most often undertaken by a nurse alone or a nurse in conjunction with a general practitioner (Hickie et al. 1998). Previous work suggests that leg ulcer patients contribute up to 20% of community nurses' workload and account for up to half of their patient contact time (Audit Commission 1999).

The most recent report of community nursing in England stated that general practitioners make over half of all referrals to community nursing services in England, hospital staff make approximately 22% and other undocumented sources 28% (Department of Health 2004). The collection of these data ceased in 2004, therefore current trends in referrals to community nurses cannot be determined.

Two UK based studies examined the management of leg ulcers in primary care (Hickie et al. 1998; Schofield et al. 2000) prior to the introduction of clinical practice guidelines. A further two recent UK studies were found that examined the care provided by health professionals across primary and secondary care within a single health district (McDermott-Scales et al. 2009; Vowden &Vowden 2009) post the implementation of the clinical guidelines. The first study, undertaken by Hickie et al. (1998) involved a postal survey of a random sample of 200 primary care practices in Scotland in 1993. All members of the primary care team including general practitioners, practice nurses and community nurses, completed the survey, although the response received varied according to the practice surveyed and the practitioner groups. Practitioner specific response rates varied from a high of 48% of GPs to 40% of practice nurses. The surveyed professionals were first asked which members of the primary care team carried out the initial assessment and who made management decisions for patient care. Second they were asked how on-going management of the wound was conducted and what sources of information they found most useful to guide management of leg ulcers.

Hickie et al. (1998) found that there were statistically significant differences between the perceptions of each discipline (general practitioner, practice nurse and community nurse) of who was carrying out the initial assessment ($p<0.01$) and which members decided upon the course of treatment ($p<0.001$). Assessment of patients commonly consisted of a medical history (94%) and examination of the wound (100%). All groups reported that treatment choice was strongly

influenced by presence of infection (99%), ulcer type (97%) and previous treatment (88%). Compression bandaging was reported as being used by 64% of practitioners, whilst monitoring of the wound was commonly reported to consist of measuring the wound (93%) and recording the amount of exudate (70%). Community nurses reported seeing more leg ulcer patients ($p<0.001$) and spending more time per week on their care than the other primary care practitioners ($p<0.001$). Different practitioners within general practice showed different temporal thresholds for referral of leg ulcer patients. Practice and Community nurses were shown to refer for a second opinion after a month or two of no improvement, whilst GPs tended to wait for at least two months if not longer ($p<0.001$). The disagreement in assessment of roles and lack of independent verification of the information provided makes interpretation of the results difficult but does suggest that different practitioners may have different approaches to leg ulcer management.

The second study (Schofield et al. 2000) explored the provision of leg ulcer care provided by practice nurses. The authors surveyed all practice nurses employed in the Hertfordshire region of England and asked about interest in, caseload and appointment times for leg ulcer management. The authors reported receiving 107 replies but did not provide sufficient detail to calculate a response rate. The study consisted of two surveys, the first finding found that 93% of practice nurses were regularly seeing patients with leg ulcers, despite this 34% reported that they did not like seeing these patients. The authors then conducted a further survey focusing on the group of nurses regularly reporting that they saw more than five people with leg ulcers per week. This study found that just over half of nurses had received training in Doppler assessment and compression bandaging. This training was reported to have come from nurse specialists and from wound care company representatives and in the majority of cases had been delivered in two hours or less. Over half of all practice nurses reported never using Doppler ultrasound whilst under 40 % reported never or occasionally using compression bandaging to treat leg ulcers. When questioned as to why they were not using Doppler ultrasound the most common responses were lack of supervised practice, equipment and confidence. When asked why they never or rarely used compression bandaging, responses were similar with common answers being a lack of supervised practice and lack of confidence.

The third study identified (Vowden &Vowden 2009), examined the management of leg ulcers by primary, secondary and nursing home care providers within a single health district located in Northern England in March 2007. Cases were found using trained nurses to complete chart audits and liaise with practice nurses. The pathology of leg ulcers was examined and most were diagnosed as venous in origin, although leg ulcers of mixed, arterial, neuropathy and unknown aetiology were also common. Reported methods of diagnosis used were visual (79.3%) and

Doppler assessment (66.4%) in addition to nursing (58.7%) or medical histories (60.6%). Despite the relatively high reported use of Doppler ultrasound assessment in this study only 49 % of measurements were used to inform treatment decisions for venous leg ulcer patients. There were differences in the assessment methods used by different practitioners with none of the patients with ulcers of unknown aetiology (n=45) attending a specialist leg ulcer clinic. Compression bandaging was commonly reported as being used to treat venous leg ulcers, with over 75% of all patients having a record of using this treatment. It remains unclear if there are differences between practitioners as results were not stratified by practitioner. The results of this study are unique as Vowden & Vowden et al. (2009) have examined the reported pathology and management undertaken by a wide variety of practitioners involved in the care of leg ulcers using trained abstractors to obtain this information from clinical records. As such the results obtained are not subject to non-response bias that may be present in other studies that have used survey methodologies and have low response rates. Despite the care taken in the case finding methodology used there was no further validation of the accuracy of the reporting of the underlying pathology of the wounds reported.

The fourth and final study identified was conducted in Ireland by McDermott-Scales et al. (2009) and evaluated the management of leg ulcers within a study of leg ulcer prevalence within a single district in Ireland by surveying a wide range of community care providers about their practice on a single day in 2007. The full detail of the case ascertainment strategy used by the authors can be found in the earlier section on leg ulcer prevalence. McDermott-Scales et al. (2009) examined two key features of the management of leg ulceration; ABPI assessment and provision of antibiotics, by survey and achieving a response rate of 97.2%. Over half of the patients diagnosed with leg ulcers (58%) had an ABPI assessment performed and just under half no recorded aetiology of leg ulceration (44%). The setting in which the leg ulcer was treated was highly related to the likelihood of the leg ulcer aetiology being recorded. Patients who were treated in general practice and mental health nursing services were less likely to receive a diagnosis of leg ulcer aetiology compared to when treatment was provided by nurses in nursing homes, addiction services and intellectual disability nursing services. The authors did not state if the use of ABPI assessment was related to an increase in the proportion of patients provided with a formal diagnosis of their leg ulcer aetiology but this certainly warrants further investigation in future studies.

In summary, there are few data sources available within primary or secondary care to accurately identify those practitioners who are most commonly involved in wound care and there is no single resource available which captures data from the full range of primary care providers such as general practitioners, practice nurses and community nurses. Indeed for some of these groups, community nurses in particular; no future national data collection is planned. This means that

information on this group, which may indeed be one of the largest care providers to persons with leg ulcers, is not available and cannot be examined.

The majority of the evaluations examined thus far collected has focussed on evaluating the management of leg ulcer patients in small areas using survey methods. These studies have been subject to two main limitations; geographic and non-responder bias. Geographic limitations make it unclear as to how representative the data collected may be of national trends and response rates to surveys were rarely reported and the responses to surveys were not validated (for example, by examining a random sample of patients' notes. Evaluation of the implementation of National Institute of Clinical Excellence (NICE) guidance across a wide range of clinical indicators has shown that the degree of implementation of guidance is highly variable, being dependent upon institutional and financial support (Sheldon et al. 2004).

It is also possible that the published studies have focussed on areas, or received the majority of their responses from practitioners, that prioritise leg ulcer services. These results may therefore represent a 'best case scenario' of the clinical experience which would lead to a health care access bias in the observed results. Given the doubts regarding the external generalisability of the results of leg ulcer management studies identified, it remains unclear if the results of studies evaluated in this review are indeed representative of routine leg ulcer care provided in the community at large.

The results of leg ulcer management studies evaluated thus far have not performed any exploration of the potential links between patient characteristics and variations in care and have performed only limited exploration of patient characteristics that may be associated with leg ulcer burden. Research from other disease area has shown that there are often wide variations in the care received by patients which has been shown to be associated with different patient and practitioner characteristics. These variations in care and disease development in other disease areas have long been shown to not occur randomly, but are more likely to be experienced by particular socio-economic or gender groups. This next section will discuss these variations in care and disease development, known as health inequalities, as well as discussing the studies that have looked at health inequalities in leg ulcer patients.

2.2 Health inequalities: definitions and policy perspectives

This section two of chapter two introduces the concept of health inequalities, and describes how this concept has been operationalised. Next an overview of current government policy regarding the reduction of health inequalities will be provided, highlighting the changes that have been made in past few decades as well as providing a general discussion of the impact of health inequalities policy on health care within the UK. Finally this section will provide a description of methods that have been commonly used to measure health inequalities.

Carr-Hill & Chalmers-Dixon (2005) describe three differing concepts of health inequalities that have been frequently used;

- Differences or variations in health between groups.
- Inequalities in health.
- Inequities or the unfairness of differences.

A useful definition for conceptualising health inequalities is '*Differences in health that are socially or economically determined rather than being due to differences between races, the sexes and people of different age'* Black et al. (1980). This definition was chosen as it distinguishes between differences that are due to factors that cannot be changed (e.g. sex and genetics) and those factors that have the potential for change (social and economic environments). It must however, be acknowledged that there are complex interactions between the age, gender and race of persons and the social and economic determinants of health.

Although average life expectancy of the UK population has been steadily increasing over previous decades these gains have not occurred equally amongst all socio-economic groups within society. For some groups in society there are slower improvements compared with the rest of the population or in some cases a worsening in absolute terms (Graham &Kelly 2004).

2.2.1 UK health inequalities policy

Since the 1980's there has been a substantial policy focus on health inequalities in the UK. A series of government reports starting with The Black Report (Black 1980) showed that differences in health status between the richest and poorest groups within society were substantial. Coming some eighteen years later, the report by Acheson (1998) highlighted the lack of evidence about how to reduce disparities in health. In response further work was commissioned by the government and The Wanless Report (Wanless 2004) gathered further evidence resulting in a total of 21 specific recommendations to reduce health inequalities. In 2005, when the EU Presidency was passed to the UK, tackling health inequalities was one of the two health policies highlighted at this time. Work undertaken included organising a summit to

discuss health inequalities in EU member states and commissioning reports to examine health inequalities in member states as well as work summarising approaches to tackle health inequalities (Wilkinson &Pickett 2006).

The progression of policy from description of the problem of health inequalities to co-ordinated governmental action to reduce health inequalities has also been echoed in policy developments in other European countries over the same time period. Despite these advances, Mackenbach and Bakker (2003) suggested that '*policymaking in this area still is largely intuitive and would benefit from incorporation of more rigorous evidence-based approaches*'.

In 2010, a new report was produced entitled 'Fair society, Healthy Lives', which documents the most recent government strategy to reduce health inequalities post the year 2010 (Marmot 2010). Many of the themes identified in this review, such as the pervasive nature of health inequalities throughout the life course and the need for cross government co-operation to reduce them are not new. What is new is the explicit introduction of performance indicators linked to policy objectives that will allow evaluation of the impact and delivery of the proposed services and policies to reduce health inequalities.

Central to the tenets of the National Health Service (NHS) is that care for all should be provided according to need and not ability to pay, and furthermore that the NHS will work to keep people healthy and reduce health inequalities (NHS 2007). The establishment of the NHS has ensured that all persons within the United Kingdom have free access to health care. Despite this universal access to health care, people at different ends of the social spectrum still have different profiles of health and disease. In 1971 Tudor-Hart (1971) described what he termed '*the inverse care law'*, to describe the way in which the availability of medical care tends to vary inversely to the need of the population served and thus further contributes to health inequalities.

Work undertaken by Shaw et al. (2005) suggests that growing societal economic inequalities are linked to growing inequalities in all cause mortality. Despite these policies it has been asserted that '*although people from low socio-economic backgrounds and with poor health use comparatively more primary-care services (which accords with their increased need for care), they are no more likely to be prescribed medication, are less likely to be referred for elective outpatient treatment, and have lower rates of elective surgery in relation to need'* (Raine &McIvor 2006).

Given the multi-factorial nature of the determinants of health, the policy response to reduce health inequalities comes from a wide variety of government departments including housing, health and local government. Exworthy (2003) provides a typology of UK policy addressing

health inequalities which provides a useful overview of the range of interventions that have been recently implemented and is shown below in table 2.3.

Table 2.3 Example of health inequality reduction policies in UK government

Domains of Policy	Examples of new policies or approaches, related to health inequalities
Life course approach: Early childhood years	Sure start programme Child poverty reduction
Area based initiatives: Focus on disadvantaged communities	Health Action Zones
Redistribution: "Welfare-to-work"	Tax Credits
Health Care	Organisational reform in the NHS Primary care trusts
Targets and performance culture	Public Service Agreements Health Inequalities targets
Structures and processes: Joined up government	Cross-cutting review of health inequalities

Adapted from Exworthy (2003)

To date, the vast majority of work examining inequalities in health care provision has examined the provision of medical services. Recent studies have shown that people attending medical practices in more socially deprived areas receive lower quality of care as measured by the Quality and Outcomes Framework (Ashworth &Armstrong 2006; McLean et al. 2006).

It is unknown whether similar differences exist with respect to nursing services. One early study undertaken in America in the late 1950's examined the social class of patients that public health nurses preferred to serve, finding the majority of nurses preferred to serve the middle and lower classes rather than the upper classes (Willie 1960). One study was found that examined the provision of practice nurses in England and Wales and found that there were fewer practice nurses in deprived areas (Hirst et al. 1998). This suggests that the inverse care law may also apply to the provision of nursing care although there is a limited evidence base for this assertion.

Looking for an explanation for the existence of inequalities in healthcare Tsuchiya & Dolan (2007) undertook a study which compared the social preferences of care provision between members of the public and NHS staff involved in care delivery. The staff groups consisted of specialists, general practitioners and practice nurses. Study participants were sent a questionnaire asking them to elicit preferences over maximising life expectancy and reducing inequalities in life expectancy between the high and low social classes. Compared with NHS staff members of the public were more likely to choose to sacrifice total health for a more equal distribution of health (Tsuchiya &Dolan 2007). The study did not examine differences in preferences between different NHS staff groups so it remains unclear if the results obtained in this study were consistent across groups.

2.2.2 Measurement of health inequalities

The status or socio-economic position of a person within a society is more than the measurement of income. Status can also be indicated by a person's education, job status, parental or partner's occupational class. The location of a person within the social hierarchy will directly determine many of the determinants of health that a person experiences throughout their entire life course.

Many different measures have been used to assess socio-economic position in studies of health. The measurements used fall into two broad categories, individual or traditional, or area level measures. Five of the most commonly encountered measures are described in detail below starting with individual or traditional measures of socio-economic position.

2.2.2.1 Individual level measures

Registrar General's Social Class

One of the earliest examples of how status was operationalised for epidemiological research in the UK is the Registrar General's Social Class Classification. This classification of an individuals' social class was designed for use with the 1911 Census. The purpose behind this measure was to search for an explanation for the differences in fertility and mortality between the industrial proletariat and the wealthier classes (Szreter 1984). The classification categorises people according to their degree of material wellbeing using their occupation (Office of Population Censuses and Surveys 1980; Bartley 2004). The Registrar Generals' Social Class consists of five different occupational categories graded from one to five. The schema is shown below in table 2.4.

Table 2.4 Schema of the Registrar General's Social Class measure

Level	Occupational class name
I	Professional
II	Managerial
III	Skilled non-manual and skilled manual
IV	Semi-skilled manual
V	Unskilled manual

(Office of Population Censuses and Surveys 1980)

The registrar general's social class classification was updated in 1921 and at each decennial census thereafter and was retained as an official socio-economic measure until 2001 (Rose &Pevalin 2001). The other official socio-economic measure used until 2001 was the Socio-economic groups' classification which is discussed next.

Socio-economic groups classification

The socio-economic groups classification was introduced in 1951 with an '*operational requirement to take into the occupational status and size of the employing organisation as well as occupation',* which Rose & Pevalin (2001) argue made this measure more theoretically sociologically based than the earlier Registrar General's Social Class measure. The socio-economic groups' classification is shown below in 2.5.

Table 2.5 Schema of the Socio-economic Groups

Level	Occupational class name
1.1	Employers in industry, commerce etc (large establishments)
1.2	Managers in central and local government, industry, commerce etc (large establishments)
2.1	Employers in industry, commerce etc (small establishments)
2.2	Managers in industry, commerce etc (small establishments)
3	Professional workers -self employed
4	Professional workers -employees
5.1	Intermediate non-manual workers - ancillary works and artists
5.2	Intermediate non-manual workers - foremen and supervisors non-manual
6	Junior non-manual workers
7	Personal service workers
8	Foremen and supervisors - manual
9	Skilled manual workers
10	Semi-skilled manual workers
11	Unskilled manual workers
12	Own account workers (other than professional)
13	Farmers - employers and managers
14	Farmers - own account
15	Agricultural workers
16	Members of armed forces
17	Inadequately described and not stated occupations

A review of socio-economic classifications in the mid 1990's then led to the development of a new measure, the National Statistics Socio-economic Classification (NS-SEC), which was an attempt to unite the best features of the registrar generals social class classification and socio-economic groups classification (Rose et al. 2005). A further aim of this new measure was to provide further explanation of the associations observed ,as there is a direct measure of employment relations and conditions as well as providing classifications for non-workers for the first time (Rose et al. 2005). The schema of the overarching categories used for the NS-SEC is shown below in Table 2.6.

Table 2.6 Overarching categories of the NS-SEC

Level	Occupational class name
L1	Employers in Large Establishments
L2	Higher Managerial Occupations
L3	Higher Professional Occupations
L4	Lower Professional and Higher Technical Occupations
L5	Lower Managerial Occupations
L6	Higher Supervisory Occupations
L7	Intermediate Occupations
L8	Employers in Small Establishments
L9	Own account workers
L10	Lower Supervisory Occupations
L11	Lower Technical Occupations
L12	Semi-routine Occupations
L13	Routine Occupations
L14	Never Worked and Long-term Unemployed
L15	Full-time Students
L16	Occupations not stated or inadequately described
L17	Not classifiable for other reasons

Education

Another individual measure that has been widely used to investigate relationships with health inequalities is educational attainment. The measure of education is intertwined with occupation as the level of education that a person achieves is often highly correlated with occupational status. Education has been measured primarily in two ways; as a continuous or categorical variable. Measured continuously researchers can examine the total number of years of education whereas measured categorically researchers can categorise peoples educational attainment based on completion of primary, secondary or further education (Galobardes et al. 2006a).

2.2.2.2 Area level measures

Area level measures of health inequalities are proxy measures of individual socio-economic position based on the characteristics of an area in which an individual lives. Data from individual measures generally come from census data and are formed using a variety of different from a variety of different variables. Two of the most commonly used measures of area level deprivation are discussed below.

Townsend Deprivation Index

The Townsend deprivation index has been one of the most commonly used measures of deprivation in studies of health. It is a measure of material deprivation of the area in which an individual lives. The Townsend deprivation index (Townsend et al. 1988) is calculated using the following domains (unemployment, car ownership, home ownership and overcrowding) from census data. It is this measure that will be used in the analysis presented in chapters five and six.

Unlike the Index of Multiple Deprivation which is described below, the Townsend deprivation index can be calculated for all countries of the UK.

Index of Multiple Deprivation

The Index of Multiple Deprivation is a relatively new measure designed and first produced in 2000 for use in England. Like the Townsend deprivation index, the Index of Multiple Deprivation is also a measure of area level deprivation. At this time of its creation in 2000 the index consisted of six different domains: Income, Employment, Health Deprivation and Disability, Education Skills and Training, Housing and Geographical Access to Services Measured at Ward Level (DETR 2000). A newer version was created in 2004 and updated again in 2007 now consists of seven domains which include; Income Deprivation, Employment Deprivation, Health Deprivation and Disability, Education Skills and Training, Barriers to Housing and Services, Living Environment, Deprivation and Crime (Noble et al. 2004; Noble et al. 2008). The measure is calculated at the geographical level of Lower Layer Super Output Area (LSOA) which comprises a mean population of 1,500 residents (Connecting for Health 2010). Although some authors have expressed concern regarding the inclusion of a health domain in the measure when trying to measure effects on health can lead to a phenomenon known as mathematical coupling. Mathematical coupling means '*that part of the relationship between two variables is due to a common component*' (Archie 1980). Empirical work undertaken by Adams et al. (2006) suggested that the removal of the health domain from the English version of the IMD measure had little effect on the association with census measures of health such as limiting long term illness.

Subsequently, specific measures have been created for use in Wales, Northern Ireland and Scotland. The domains included in these indices differ slightly to those included in the English version and are measured at different geographical units in some of the countries (Northern Ireland Statistics and Research Agency 2005; Welsh Assembly Government 2008; Donnely 2009). The English measure will be used in the analysis presented in chapter four.

There is considerable debate regarding the relative importance of area of residence (contextual effects) or the socio-economic position of the person living in the area (compositional effects) and the relationship with health outcomes. The results of a systematic review of multilevel analyses that compared the effects of individual and area level measures demonstrated that the majority of included studies found that there were associations with area based measures and health outcomes, even after adjustment for individual measures of socio-economic position (Pickett &Pearl 2001). Further work suggests that many measures of area level deprivation are highly correlated with health outcomes and behaviours independently of individual level socio-

economic measures. Evidence for the independent effect of measures of area level deprivation have been shown for associations with a wide range of health outcomes including self reported health, lung function, smoking habits and coronary heart disease (Shohaimi et al. 2003; Shohaimi et al. 2004; Adams et al. 2005; Lawlor et al. 2005), even when other variables measuring socio-economic position such as education were adjusted for.

The earlier systematic review of prevalence studies concluded that most leg ulcer patients are older women and men (Graham et al. 2003a). Traditional measures of socio-economic position may be limited in the older cohort of people with leg ulcers. First, the applicability of socio-economic measurements based on occupation may be limited given that most persons who develop leg ulcers are past retirement age and have left the labour market. Second, there may be a sizeable proportion of women who may have never entered the labour market and therefore rely on accurate measures of their husbands occupational status. Finally, education may not work as well as an indicator in the elderly as societal norms and expectations of education have changed over time. British and European populations of an older age group were more likely to have left school with no qualifications meaning that there may little differentiation between more and less advantaged groups using these measures (Grundy &Holt 2001). Given these concerns over socio-economic measures in the elderly Grundy & Holt (2001) sought to specifically identify the best socio-economic indictor for use in the elderly population by evaluating the relationship between self reported health and seven different measures of socio-economic position. Their work concluded that the best measure was achieved using a combination of either education or occupational social class and a measure of deprivation, such as the Townsend Deprivation Index, although there may be limitations given that only 55-75 years were included in their analyses (Grundy &Holt 2001). In contrast O'Reilly (2002) used longitudinal data to find that uptake of benefits was the strongest predictor of mortality in those aged over 75 years although area based measures such as the Townsend score were found to perform better than individual measures of social class such as education. These results were later confirmed by Grundy & Sloggett (2003).

There is further evidence from the results of studies conducted in the US by Krieger et al. (1992) that area based measures may be adequate proxies for individual socio-economic data if there is a lack of individual data. It is proposed that there are several advantages to using area rather than individual measures for health research particularly in the majority elderly population with leg ulcers. First, traditional measures of social class such as occupational social class for women were often based on the occupation of her partner. Given changes in women's working patterns and earnings within families the assumptions underlying these methods may no longer be universally valid in today's society where many women now have higher earnings than their partners (McFadden et al. 2009). Second, there are further problems using occupational social class when

examining the unemployed and retired persons as they are not in current employment and may have had many different occupations over the lifecourse. Third, changes over time in income and educational classification schemes make the exploration of time trends using these data difficult.

Area based measures of socio-economic position are estimated based on the area of residence linked to their postcode, and do not therefore require patients to disclose sensitive information or indeed information that they would not routinely provide their health care providers with. Another advantage for research is that area based measures can be aggregated, in the form of a fifths or deciles of deprivation, which also has the advantage of producing a measure which is far likelier to maintain the anonymity of the research participant.

Section two of chapter two has provided an overview of some of the more commonly used measures of health inequalities as well as providing a brief overview of government policy for their reduction. In section three, the literature that examined both health inequalities and leg ulcers will be reviewed.

2.3 Health inequalities and leg ulceration

2.3.1 How might SEP influence both the development and healing in leg ulceration?

Venous and arterial diseases are both influenced by a common set of risk factors including diabetes mellitus, obesity, metabolic syndrome and increasing age (Prandoni et al. 2003). The metabolic syndrome consists of central obesity plus two of any of the following symptoms; raised triglycerides, reduced HDL cholesterol, raised blood pressure or raised fasting plasma glucose (Grundy et al. 2004). Both the prevalence of type II diabetes (Evans et al. 1999) and the prevalence of metabolic syndrome (Chandola et al. 2006) have been shown to have an inverse socio-economic gradient, with persons of low socio-economic position having higher disease burdens compared to persons of high socio-economic position. Smoking is also positively associated with diseases that underlie leg ulceration, such as lower limb venous insufficiency (Gourgou et al. 2002) and lower limb peripheral arterial disease (Willigendael et al. 2004).

For more general risk factors for the development of leg ulceration, specifically smoking and obesity, different gender related inequalities have been shown to exist. In women, a negative association has been observed between socio-economic status and obesity, with rates of obesity found to be more prevalent in poorer groups of women (Law et al. 2007). Rates of smoking are shown to be higher in the lower socio-economic classes compared with higher socio-economic classes in both men and women (Power et al. 2005).

Another mechanism by which social factors are hypothesised to be related to leg ulcers is via activation of stress pathways, which may result in impaired healing. There is a large body of evidence demonstrating associations between exposure to stress and delayed healing of acute wounds, such as mechanically created suction blisters (Walburn et al. 2009). Although limited, there is also some evidence that stress may be associated with healing of chronic wounds, such as leg ulcers (Cole-King &Harding 2001). There are several theories that have attempted to explain the physiological mechanisms linked to stress that result in impaired wound healing. The first suggests that stress can activate the hypothalamic-pituitary-adrenal and the sympathetic-adrenal medullary axes, classically referred to as the 'flight or fight response', which in turn activate gluco-corticoid hormones which then lead to delayed wound healing (Godbout &Glaser 2006). Second, there is evidence that certain psychological conditions, such as depression and anxiety may cause physiological changes that impact upon hormonal and immunologic function which again lead to impaired wound healing (Vileikyte 2007).

2.3.2 History of studies investigating links between SEP and leg ulceration

The role of socio-economic factors in leg ulceration has been examined in four studies to date. One study examined the socio-economic distribution in a subset of a prevalent population of leg

ulcer patients(Callam et al. 1988), one used a case-control design to examine the likelihood of leg ulcer healing according to the socio-economic status of the patient (Franks et al. 1995b) and two examined the association of leg ulceration with social factors, including both socio-economic position and broader social conditions (Fowkes &Callam 1994; Moffatt et al. 2006).

The earliest study of the distribution of leg ulceration by social class was undertaken by Callam et al. (1988). Examination of the socio-economic distribution of leg ulcer patients was then conducted using a sample of 600 patients, from the 1477 patients identified in an earlier prevalence study (Callam et al. 1985). These 600 patients had agreed to a further interview and examination of their leg ulcer (Callam et al. 1988). Patients provided details of their occupation, which was classified using the Registrar General's Social Class, as well as providing information regarding both duration and number of episodes of leg ulceration. No difference was seen in the distribution of social class in the leg ulcer population compared to the total population within the study area. However, patients of lower socio-economic status were observed to have had a greater number of leg ulcer episodes and longer leg ulcer duration compared to higher socio-economic status patients (Callam et al. 1988). The authors did not report how retired or unemployed people were classified which is significant given that these groups comprised 80.5% of the sample. The authors felt that the subgroup examined was representative of the total sample with respect to age, sex, source of referral and geographic distribution. No examination of the socio-economic representativeness of the sub sample compared to the total leg ulcer population identified was performed.

A case control study conducted by Fowkes & Callam (1994)compared the socio-economic status of leg ulcer patients using a further subgroup aged 55-74 years from the study by Callam et al. (1988) with healthy controls from another study (Fowkes et al. 1991) (i.e. not from the same population as the cases). The authors found a statistically significant difference between the groups in terms of the distribution of social class with leg ulcer patients more likely to come from the lower social classes compared with the control group ($p<0.001$). It is unclear if this result was due to the different socio-demographic profile of the different populations used to obtain cases and controls (i.e. differences between Edinburgh and the entire Lothian and Forth valley populations). The analysis was adjusted for age and sex. The results of this study must however be interpreted with caution as the results may be biased by the selection of the control group who were from a different source population as the case group (Rothman &Greenland 1998).

A further case control study compared the Standard Occupational Classification (1990) of leg ulcer patients to control patients, whilst also examining the effect of ethnicity, marital status, living status and social support (Moffatt et al. 2006). Cases were identified from an earlier

prevalence study (Moffatt et al. 2004) and controls were sourced from general practices in the same geographic area of London where the prevalence study was undertaken. Insufficient detail was provided in the publication to determine if the cases and controls were sourced at the same time. Cases and controls were matched by age and sex. Moffatt et al. (2006) found that leg ulcer patients were more likely to have Afro-Caribbean ethnicity (OR 8.0), social class IV and V (OR 2.82), never married (OR 2.98), live in rented housing ($p<0.001$), have a mobility deficit ($p<0.001$) and have poorer social support ($p<0.05$) compared to controls without leg ulcers.

Finally, one study examined the influence of socio-economic status on leg ulcer healing (Franks et al. 1995b). This study included a consecutive series of patients who had been treated at a specialist leg ulcer clinic in London over a six month period, comparing the socio-demographic characteristics of those patients who did, and did not heal, over a 12 week period. The study found that lack of central heating OR 2.27 (95% C.I. 1.11-4.55), rather than social class as measured by occupation OR 2.67 (95% C.I. 0.81-8.85), was statistically significantly associated with a venous leg ulcer that had failed to heal within 12 weeks using a standardised treatment regime(Franks et al. 1995b). The analysis controlled for ulcer size, duration and mobility, all known to influence the healing response. However, the study was geographically limited, to London and had a small sample size (n=168) with wide confidence intervals around the estimates produced, suggesting that it may have underpowered to find differences should they exist (Franks et al. 1995b).

In summary, three of the four studies examining the effect of socio-economic status used methodologies that have relied upon health professionals to provide details of the leg ulcer patients that they are currently treating. In only one of these studies (Callam et al. 1988) was the response rate of the health professional reported, and in no study was any further validation of the case finding methodology performed (i.e. to check that the information provided by health professionals was accurate). In one study the cases consisted of all patients treated at single clinic (Franks et al. 1995b). The way in which social class was measured varied throughout the studies reflecting the different measures that were available at the time when studies were conducted. Callam et al. (1988) and Fowkes & Callam (1994) used the Registrar General's Classification from 1981 and both Franks et al. (1995b) and Moffatt et al. (2006) used the 1990 socio-economic classification from the Office of Population Censuses and Surveys.

The results of these studies suggest that there may be health inequalities, in both the prevalence and severity of leg ulceration, whilst the results do not provide evidence of causality as they were all based on the results of cross sectional data the results do suggest that associations exist. The one study that examined healing did not find differences by social class, but by central heating,

which may be a proxy for poor quality housing (Franks et al. 1995b). However, the different results of studies are difficult to interpret given that there are differences in the way socio-economic position has been measured throughout the studies, the age groups of patients measured and the methods employed to undertake these studies.

The interpretation of results is further made difficult due to changes in the prevalence of risk factors. For example in the two London based studies where central heating was measured the proportion of patients not having access to central heating had dropped by 50%, most likely reflecting changes in housing policy over this time period (Franks et al. 1995b; Moffatt et al. 2006). None of the authors examined whether there were differences in care received by socio-economic position which may have contributed to the elevated prevalence rates obtained. Additionally the cross sectional study designs used do not allow for causation to be established merely suggesting that there is an association between social class and prevalence of leg ulceration. These studies indentified many risk factors for the development of leg ulceration. The literature review did not locate any studies that have examined the potential effect of socio-economic differences in risk factors on the subsequent development of leg ulceration. It is further conceivable that the results identified may be the result of reverse causation. In this context reverse causation would mean that the development of a leg ulceration caused a person to have a negative change in occupational social class. It would therefore be the ulcer that caused a change in socio-economic position and not low socio-economic position that resulted in the development of leg ulceration.

These factors will be discussed further in the next section and potential theoretical explanations for these results will be provided by discussion of theories of health inequalities.

2.3.3 Theoretical explanations for results of studies examining health inequalities in leg ulceration

Several theories of health inequality may explain socio-economic variability of leg ulceration, for both the incidence and prevalence of the condition as well as the prognosis. These theories will be discussed in turn below.

Material Hypothesis

The material hypothesis supposes that it is lack of resources which causes health inequalities. The study by Franks et al. (1995b) demonstrated that healing was less likely to be achieved when patients' homes did not have central heating. While not a specific risk factor in itself, lack of central heating may be a marker for poorer quality of housing which may predispose patients to a range of additional risk factors which may exacerbate the patients' inability to heal. There is some evidence that warmer wound temperatures may contribute to increases in healing rates of

wounds (MacFie et al. 2005). However results of clinical trials using warming therapies in chronic wound patients have not yet provided conclusive evidence of their effectiveness (Kloth et al. 2002).

In the second study which examined central heating as a possible explanatory variable, no association was observed with having a leg ulcer (Moffatt et al. 2006). However, by the time of the second study the proportion of people not having central heating had reduced by 50% suggesting an overall rise in the quality of housing. It is of further interest to note that in 1997 winter fuel payments were introduced as a universal benefit for householders aged 60 years and over (Phillipson &Scharf 2004).

Another way in which material factors may be associated with leg ulcers is through diet. Poor mobility, isolation and low income have been associated with low nutrient intakes in elderly persons with leg ulcers (Lewis &Harding 1993). The direction of causality for diet causing leg ulcers however, has not been established. The evidence to date for dietary supplementation (using oral zinc supplementation) to increase healing rates of leg ulcers has not provided conclusive evidence of effectiveness (Wilkinson &Hawke 1998; Stansby 2000).

Cultural Behavioural Hypothesis

Cultural and behavioural explanations provide an alternative perspective to the material hypothesis, arguing that it is the direct behaviours associated with being a member of a particular social class that contribute to health inequalities. There is much evidence from the wider literature of health inequalities of the unequal distribution of risk factors according to socio-economic position.

Two risk factors for the development of leg ulcers, varicose veins and lower extremity arterial occlusive disease, have both been shown to be associated with multiple pregnancies compared with nulliparous women (Stansby 2000; Holzer et al. 2007). Multiple pregnancies have been decreasing, with overall fertility rates in England and Wales declining in the last fifty years dropping from a high of 2.93 per woman in 1964 to 1.95 children per woman in 2009 (Office for National Statistics 2010a). Work undertaken using data from the Millennium Cohort Study has shown that the age at which women have their first child is socially patterned, with women from lower socio-economic groups starting their families at an earlier age than women from higher socio-economic groups (Hawkes et al. 2004). Examination of a number of cohort studies showed that completed family size has declined at a greater rate in families with mothers who have higher educational qualifications compared to mothers who left school at age 16 (Ratcliffe &Smith 2006). It is likely therefore that the risk factor of multiple pregnancies is greater in women of lower socio-economic position.

For two of the behavioural risk factors associated with diseases that underlie leg ulceration; obesity and cigarette smoking, there are clear links with socioeconomic status, although only for females in the case of obesity (Law et al. 2007). These results point to a potential aetiological pathway for the development of leg ulceration that produces a greater impact on persons of lower socio-economic position due to differences of the distribution of the behavioural risk factors. Work conducted by Shankar et al. (2010) using the English longitudinal study, has further shown that older adults of lower socio-economic position are more likely to report multiple unhealthy health behaviours including smoking, drinking and sedentary lifestyles compared to their higher socio-economic position peers.

One final impact of cultural norms that may actually contribute to a decrease in development of leg ulcers is the trend for women to have smaller families. Throughout the 20th century family sizes have fallen to an average of 1.7 children from a previous average of 3.5 children (Hicks &Allen 1999). This trend for smaller family sizes is not consistent amongst different ethnic groups as different cultural norms exist. Women of Pakistani and Bangladeshi ethnicity have been highlighted as two ethnic groups that have higher than average fertility rates (Berthoud 2000). The influence of ethnicity on the risk of leg ulcers is difficult to study using routine data, given the lack of routine ethnicity reporting in primary care. Although the risk factor of high numbers of pregnancy is on average is decreasing throughout the 20th century, this reduction in risk may be negated if trends in other competing risk factors, such as obesity continue their upward trends.

Psychosocial Hypothesis

Psychosocial explanations of health inequalities focus on a hypothesis that health inequalities are created by '*economic and social circumstances affecting health through the physiological effects of their emotional and social meanings and the direct effects of material circumstances*' (Marmot &Wilkinson 2006).

There is some evidence that stress influences wound healing (Kiecolt-Glaser et al. 1995), and that stress may also have psychosocial associations with an individuals' socio-economic status(Brunner &Marmot 2006). Research that has examined the relationship between exposure to stress and wound healing has been primarily focussed on the relationship with acute wounds in otherwise healthy individuals. An example of this type of research is shown by Kiecolt-Glaser et al. (2005) who examined the effect of hostile marital interactions on the healing of acute wounds in 42 couples. In this study all couples had a suction blister wound created and were assessed whilst interviewed to gauge the extent of hostility in their interactions. Wound healing was assessed daily up to 8 days and then again 12 days post administration. Couples with greater level of hostility were found to heal at slower rates than their less hostile married peers.

Confirmatory research findings for the psychosocial hypothesis were also found in a recent systematic review, with 17 of the 22 studies included showing a negative relationship between psychological stress and wound healing, or biomarkers of wound healing in acute and chronic wounds (Walburn et al. 2009). Most studies examined in the systematic review examined experimental wounds, seven assessed clinical wounds and one assessed chronic wounds. The evidence of the relationship between stress and wound healing is therefore strongest for experimental wounds, as the studies examining these wounds were more rigorous, had larger sample sizes, and controlled for a greater range of potential confounders.

The one study included in the systematic review by Walburn et al. (2009) that examined chronic wounds, examined the effect of psychological factors in patients with leg ulcers and so will be discussed separately. The study by Cole-King and Harding (2001) included 53 patients attending a wound healing centre who had chronic leg ulcers of at least three months duration. Assessment of levels of anxiety and depression was conducted using a self completed Hospital Anxiety and Depression scale (HADS). The rate of wound healing was then assessed by the clinician in charge of the clinic who was blind to the score of the HAD test. Due to the lack of standardised assessment available to measure wound healing this study used a five point scale to assess wound healing that ranged from 1 healing well to 5 not healing. The results of these analyses showed that there was a statistically significant relationship with HAD scores, indicating that anxiety and depression were associated with delayed leg ulcer healing.

One further study published subsequent to the systematic review by Walburn et al. (2009) examined the role of stress and coping styles on healing of diabetic foot ulcers. Vedhara et al. (2010) recruited 93 patients with neuropathic or neuroischaemic diabetic foot ulcers from specialist podiatry clinics in secondary care. Patients completed the HAD questionnaire to determine levels of anxiety and depression and the Medical Modes coping questionnaire to determine levels of confrontation, avoidance and acceptance-resignation coping styles of patients. In addition to completing these two questionnaires patients also provided cortisol and wound fluid samples at baseline. Wound size was measured at baseline and rates of healing were assessed at 6, 12 and 24 weeks and all patients received a standardised treatment regimen. Analysis adjusted for predictors of ulcer healing indicated that patients with confrontational coping styles, '*characterised as being more controlling, competitive and extroverted*' were associated with a statistically significant reduction in the odds of healing over 24 weeks (Vedhara et al. 2010). Low evening measures of cortisol and high precursor levels of MMP2 (a physiological marker and mediators of connective tissue remodelling obtained from the wound fluid sample) were both shown to be

associated with healing at 24 weeks. Depression as defined by the HAD score was shown to be associated with smaller changes in foot ulcer size over the study period.

Findings by Margolis et al. (2004b) provide contrary evidence of the relationship between depression and venous leg ulcers than those observed in the earlier study conducted by Cole-King et al. (2001). Using a retrospective cohort design and data from general practice Margolis et al. (2004b) examined the co-morbid conditions that were reported in the primary care database records in the six months prior to incident diagnosis of venous leg ulcers. Although many conditions, including cellulitis, congestive heart failure and peripheral vascular disease, were found to be associated with the development of venous leg ulcers, prior depression showed no statistically significant relationship with the development of venous leg ulcers, OR 1.23 (95% C.I. 1.03-1.46).

There are several reasons why there are likely to be differences in the findings of Walburn et al. (2009), Vedhara et al. (2010) and Margolis et al.(2004b). First Margolis et al.(2004b) were looking at conditions that were recorded in patients' database general practice records prior to the development of leg ulcers. These results appear to suggest that the development of leg ulceration is associated with the development of adverse psychological circumstances. It is possible that the true rate of depression in the general practice population is higher than that observed by Margolis et al. (2004b), as it has been highlighted that only 50% of patients are properly diagnosed as having depression by primary care providers (Stromberg et al. 2008). Whilst available evidence indicates that depression may impact upon healing of both leg and diabetic foot ulcers, there is as yet, no evidence that it provides an aetiological pathway to leg ulcer development.

Stress has also been studied as a risk factor for diseases that underlie leg ulceration and as a causative agent that contributes to impairment in healing of both acute and chronic wounds. One study examining the relationship between stress and subsequent hospital admission as a result of varicose veins in males was located. This study found an association between medium and high baseline measures of stress using the Reeder Stress Inventory and admission for lower limb varicose veins over 20 years following screening, even after adjusting for age, social class and risk factors such as smoking and alcohol consumption (Metcalfe et al. 2003). No studies were found examining these associations in females so it remains unclear if this observation is specific to the male gender only.

Whiteman et al. (2000) examined whether personality traits or socio-economic factors were predictive of progression of atherosclerotic disease, which may underlie peripheral arterial disease using a cohort study design. This study examined the Ankle Brachial Pressure Index (APBI) of

1592 people at baseline and at five years. This study found that baseline scores in APBI were associated with personality and social factors and that change in APBI (i.e. a lower score indicating the presence of greater arterial disease) was negatively correlated with age in both males and females. Regression models showed associations between heavier smoking, older age, higher cholesterol and lower APBI at five years of follow-up. For men only, there was an association with deprivation, as well as the aforementioned explanatory variables and worse APBI at five years.

Conclusions

Only four studies were found that examined the contribution of socio-economic factors to both the prevalence and prognosis of leg ulceration. Although the results were not entirely consistent, three of the four studies found positive relationships between measures of socio-economic position and leg ulcers, in either the prevalence or severity of leg ulceration. Existing studies on the relationship between leg ulceration and socio-economic position do not provide robust evidence of association or causation. However, there are many reasons to suggest that such an association may exist. There are potential aetiological pathways for health inequalities to manifest themselves in persons with leg ulceration that warrant further investigation.

Future studies examining the contribution of socio-economic factors to health inequalities need to be undertaken in larger patient populations. Future studies also need to take account of the role of health care providers in contributing to, or to potentially ameliorate health inequalities, that may result from differences in the provision of care by patient socio-economic position. It is known that the new General Medical Services contract takes no account of deprivation or ethnicity on target levels (Raine &McIvor 2006). Primary care data provides a unique opportunity to explore these areas further in a timely manner and provide much needed evidence to improve practice and policy decision making.

The results of the studies that examined stress and wound healing indicate that there are likely to be complex neurophysiological links between stress, psychosocial factors, deprivation and a range of adverse health outcomes, including wound healing. Existing evidence on the relationship between these factors and leg ulcer wound healing is still lacking, with only one cross sectional study undertaken to date. The results from this one cross sectional study do not prove evidence of causation but do indicate that an association exists between depression, stress and leg ulcer healing. The impact of psychological approaches as a further therapeutic strategy to contribute to improved leg ulcer healing rates merits further investigation in randomised controlled trials so that evidence of the effectiveness of this approach can be established.

The results of studies demonstrating that there are associations between stress and wound healing may provide a plausible explanation for the results observed by Callam et al. (1988) and Franks et al. (1995a) which showed that lower SES leg ulcer patients were found to have conditions that were both more severe and less amenable to healing.

2.3.4 How my research will add to existing knowledge

At present the largest study of leg ulceration incidence and prevalence undertaken in the UK to date was limited to the exploration of the burden of venous ulceration in the elderly only. This study conducted by Margolis et al. (2002) shows that there is further potential to use general practice databases for the study of leg ulcer disease burden and management, given that leg ulcer data in the GPRD was shown to be sufficiently accurate and valid. New general practice databases, available subsequent to the study by Margolis et al. (2002) now provide the opportunity to examine the effect and relationships between proxy indicators of socio-economic position, such as the Townsend deprivation index and leg ulcer disease burden and management. This analysis will contribute to an updated understanding of the role of socio-economic position and the development of leg ulceration.

Future studies of health inequalities in leg ulceration will create an evidence base of direct use to both the NHS and policy makers to inform the future implementation of projects to tackle health inequalities in the area of leg ulcer care. This research will also provide much needed data regarding the quality of care provision for leg ulcer patients in general practice. This is an area that has been under researched, particularly given the numbers of patients using these services and the health services costs associated with the provision of these services.

In addition further work in this area will provide continuing impetus to tackle the modifiable risk factors that contribute to the development of this chronic and debilitating condition. Work undertaken in this thesis will also allow examination of the relationship of socio-economic position and healing, as well as exploring the socio-economic representativeness of leg ulcer patients included in clinical trials.

It is proposed that the thesis will add to existing knowledge in a number of ways.

- Determine if socio-economic gradients are observed in both the incidence and prevalence of leg ulceration (when adjusted for age and sex).
- Will explore whether guideline recommended initial assessments, treatments and referrals are provided to patients with leg ulcers within general practice. Further examination will be undertaken to explore potential differences in care provided

according to patient level variables (age, sex, pathology, deprivation) and practice level differences (area deprivation of practice, size of practice.)

- By quantifying differences in risk of healing (or not healing) by socio-economic position.
- By gaining a greater understanding of the socio-economic position of patients included in clinical trials and exploring what impact this may have on the external representativeness of trials.

3.0 Measuring disease incidence and prevalence: a comparison of the burden of leg ulceration using two general practice databases.

3.1 Introduction

Establishing the current burden of leg ulcer disease within the UK population is problematic for several reasons. First, there are no mandatory requirements to collect these data, nor are there any specialist disease registers for this condition. Second, treatment for the condition is provided by a wide variety of practitioners in community, primary, and secondary care although no central data collection of these activities is available from providers. Of these treatment providers, centralised data collection of the number of admissions and patients treated is only available for those patients admitted to hospital for leg ulcer treatment. As hospitalisation of leg ulcer patients is not part of routine clinical management this approach to obtaining burden of disease data will lead to a severe underestimation of the impact of this condition.

Despite the large numbers of patients treated in primary care, there is little routine data collection of the activities undertaken either at a country or national level. There is certainly not the mandatory collection of activities and services provided that hospitals are expected to report as part of Hospital Episode Statistics (HES) (Health and Social Care Information Centre 2010). One notable exception is the routine data collection of primary care activities for the management of conditions forming part of the Quality and Outcomes Framework (QOF). The '*QOF is a voluntary reward and incentive scheme detailing practice achievements in a range of clinical and non-clinical domains'(*The Information Centre 2004). Whilst QOF data provides prevalence data of the included conditions there are some limitations that affect the epidemiological inferences that can be made. First, the type of denominator data for a practice is limited. This means that it is not possible to standardise the rates of any disease relative to the practice that they attend. Second, it is not possible to know the amount of patients that practices have chosen to exempt from QOF reporting so it is not possible to identify the proportion of patients for whom data may be missing (ERPHO 2005).

The care of leg ulcer patients does not form part of the QOF, so no leg ulcer data is collected nationally under this scheme. Additionally, no routine data collection of the work of community nursing is currently undertaken. Previously some limited work was undertaken. The last of these series of reports was published in 2004 and related to data on community nursing consultations that took place in the years 2003-4 (Department of Health 2004). Although the reports published in this series provided extensive information concerning the number of patient contacts made by community nurses, they did not contain information regarding the clinical work conducted

during these visits. Previous work suggests that a large proportion of the workload of community nurses is the care of leg ulceration (Lees &Lambert 1992). The trends in this workload over time remain unknown.

The most recent UK based estimates of prevalence are based on data collected in 1998 (Moffatt et al. 2006) and the most recent incidence results come from data that were collected from 1988 until 1996 (Margolis et al. 2002). Since the mid to late 1990's the evidence base for the care for persons with leg ulceration has increased with the introduction of three separate UK guidelines for the management of leg ulceration (CREST 1998; SIGN 1998; RCN 2006). The impact of these guidelines on disease burden or improvements in leg ulcer management has yet to be evaluated in population-based studies.

A systematic review of leg ulcer prevalence studies, undertaken by Graham et al. (2003a), found that most estimates produced in these studies were based on data from distinct geographical regions using non-validated survey response data obtained from health professionals. Published after the search date of the earlier systematic review, a study of the incidence and prevalence of venous leg ulceration was undertaken. Margolis et al. (2002) used the General Practice Research Database (GPRD) determine incidence and prevalence of venous leg ulceration in the population aged 65 years and over from 1988 to 1996. The GPRD is a database containing the longitudinal records of over 10 million patient consultations from the United Kingdom (July 2007 figures). This study confirmed that large numbers of patients were seeking treatment for leg ulceration in general practice, making the study of leg ulceration feasible in this setting. The authors also undertook an assessment of the validity of coding of venous leg ulceration in the GPRD and found it to have high levels of sensitivity and specificity (Margolis et al. 2002).

The work undertaken by Margolis et al. (2002) demonstrated the potential of using primary care databases to produce valid estimates of leg ulcer disease burden. There is further capacity to expand the analysis using both the GPRD and other primary care data sources to expand the study of leg ulcer burden to a wider population and a wider examination of leg ulcer sub types.

Comparing the results of different leg ulcer disease burden studies is problematic due to the wide range of populations included and the temporal periods studied. The estimates provided by earlier burden of disease studies, known as crude estimates, provide results that are applicable to the populations in which they were studied. However the comparison of crude rates between studies may mask differences due to differences in age structures between the populations compared. One strategy that has been widely used to remove such bias and enable comparisons between populations and between different time periods is to perform direct standardisation.

Direct standardisation allows the rates from two studies (or populations) to be compared by choosing an appropriate reference standard to which the rates from different age stratas of the two populations can be compared. This eliminates the confounding effects caused by differences in age distributions between populations.

Earlier work undertaken using the GPRD has confirmed that large numbers of patients with leg ulceration are being treated within general practice (Margolis et al. 2002). Although it is often claimed that the GPRD represents the 'gold standard' of primary care data(GPRD 2010), it remains unclear whether estimates obtained in the study by Margolis et al. (2002) are comparable with other newer sources of general practice data. For other clinical conditions, such as musculoskeletal and respiratory disease, differences in prevalence rates have been observed when comparing the estimates from GPRD to those produced using other data sources (Hansell et al. 1999; Jordan et al. 2007).

This study will use another general practice database, The Health Improvement Network (THIN), to perform a comparison of incidence and prevalence rates of leg ulcers encountered in general practice. No studies were located that examined the comparability of rates of leg ulcers between these databases. Neither were any studies found that compared estimates of any other clinical conditions. There is a reasonable expectation that these two databases may produce comparable results given that over half of the practices that contribute to the THIN database also contribute to the GPRD. However, this has never been demonstrated empirically (The Health Improvement Network 2007).

By undertaking incidence and prevalence studies using data sources that have national coverage, the current burden of leg ulceration in the UK population can be estimated. In addition further hypothesis generation and testing can occur, allowing exploration of the effect of different risk factors, treatment strategies and time periods on the rates of the condition.

3.1.1 Background to the GPRD

The GPRD is arguably one of the best known sources of UK primary care data available for research and has been used extensively to conduct disease epidemiology, pharmaco-epidemiology and drug safety studies. Furthermore the codes used to identify patients in the database with particular disease have been subject to a multitude of validation studies (Gelfand et al. 2005). However, a number of different versions of the database have been used to conduct these studies. For example, a distinct version of the GPRD is used and maintained by the Boston Collaborative Drug Surveillance Program. This version of the GPRD does not include data from over half of the original practices that contributed data. This was because certain practices were

unable to provide validation services, switched to other computer systems or have asked to have their data removed from the database (Jick et al. 2003). Two further versions of the GPRD are known to exist. First, there is a version provided by EPIC, which is a static version of the database containing data collected from 1988 to 2002. Second, there is a version provided by the MHRA, the current administrators of the GPRD which is constantly updated and contains information from 1987 through to the current day.

Research has been undertaken which combined the patient populations of both the EPIC and MHRA versions of the GPRD for the purposes of pharmaco-epidemiological research. Vroom (2008) found that there was considerable overlap between these two versions, but did not examine differences that may exist between these two versions of the GPRD. Unpublished data provided by Professor DeVries at the University of Bath illustrates the number of contributing practices and the numbers of patient years available for analysis in both the MHRA and EPIC versions of the GPRD. These can be seen below in Figure 3. and Figure 3..

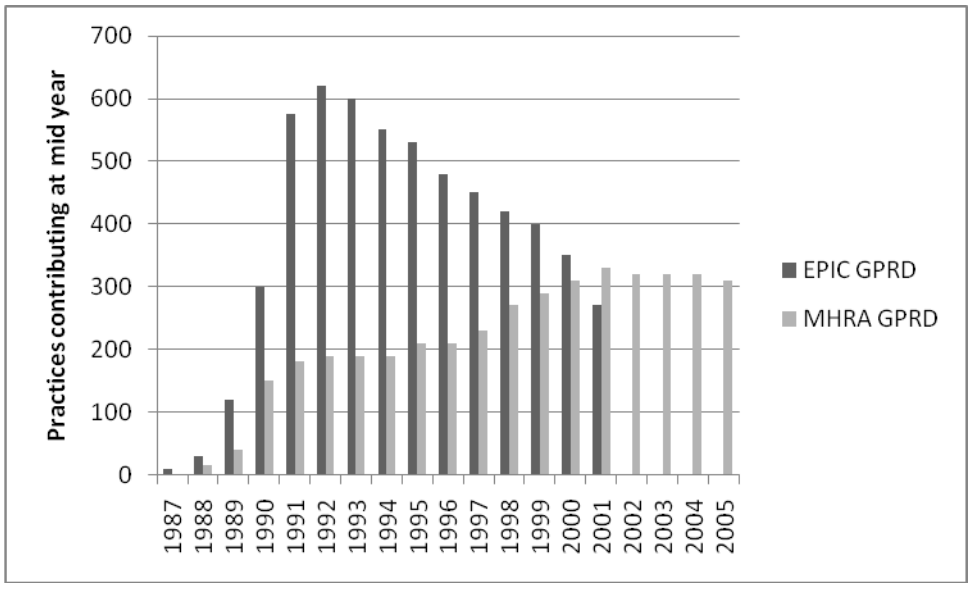

Figure 3.1 Numbers of practices contributing to the EPIC and MHRA version of the GPRD at mid year

Figure 3.1 above shows that there were substantial variations in the number of practices contributing to both versions of the database over the years 1989 to 1999. In the EPIC version of the GPRD the number of practices contributing data halved from over 600 practices contributing in 1991 to fewer than 300 by 2001. In the MHRA version of the GPRD the changes in the numbers of contributing practices was reversed. In the MHRA version numbers increased from fewer than 10 practices in 1987 to 330 practices by 2001.

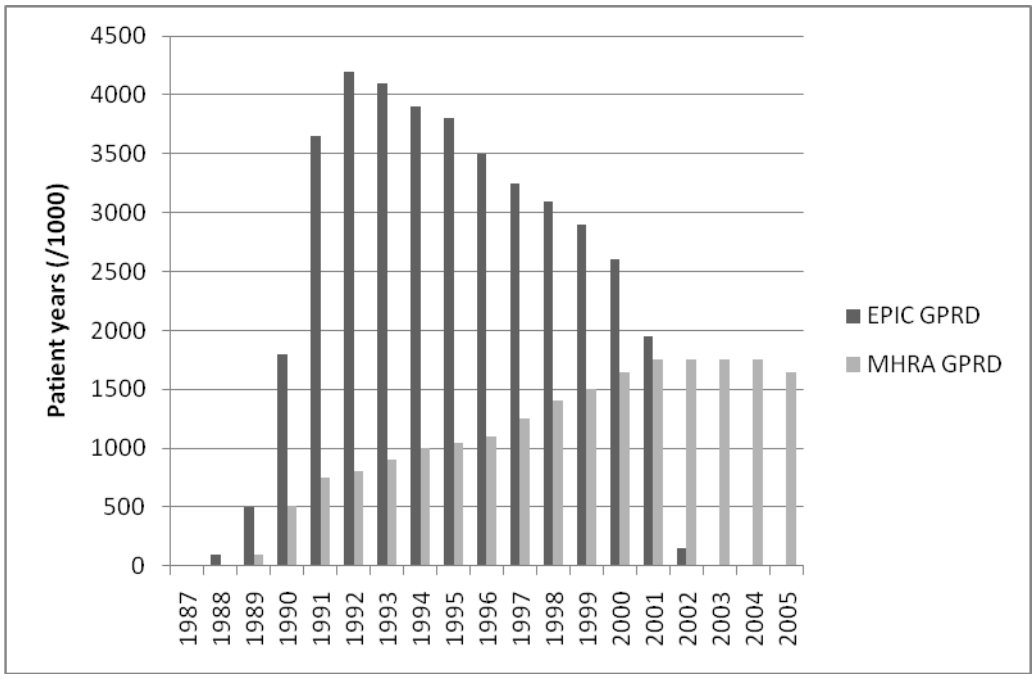

Figure 3.2 Comparison of available person years of analysis in EPIC and MHRA versions of the GPRD.

As can be seen in Figure 3.2 above, there were substantial differences between the numbers of patient years available for analysis in the two different version of the GPRD. This is consistent with the earlier findings which showed that there were greater numbers of practices contributing data to the EPIC version of the GPRD than to the MHRA version.

3.1.2 Background to newer primary care data resources

Since the creation of the GPRD, two other large general practices databases have been established. The first of these databases, the QResearch database is administered by the University of Nottingham obtaining data from practices using the EMIS clinical computer system (Hippisley-Cox et al. 2007). The second database is The Health Improvement Network (THIN), which is run as a commercial partnership between EPIC and In Practice Systems (INPS) (The Health Improvement Network 2007). The usage of both of these databases is restricted to the conduct of epidemiological, drug safety and the treatment and prevention of disease studies.

The QResearch and THIN databases both contain anonymous longitudinal patient records that are continually updated. Available data includes patient demographic details such age and sex, reported diagnoses and symptoms, prescription issued, diagnoses from specialist referrals, hospital admissions and the results of laboratory tests. Additionally, both databases used the Read classification system to code clinical, referral and some therapeutic events. These same coding systems are used by the GPRD to code clinical therapeutic and referral events.

Additionally, the GPRD also has OXMIS codes which were historically used to code events but are no longer in current use.

Whilst both databases show potential for research there were limitations to the conduct of research using the QResearch database. Unlike the THIN database the QResearch database administrators did not provide Townsend scores at patient level, only for aggregated datasets. As only descriptive analyses could be undertaken using the QResearch database there would be very limited evidence that could be gleaned from these data. Therefore the decision was made to use the THIN database so that more informative analyses of socio-economic data could be undertaken.

3.1.3 Rationale for current study

There is still much potential for exploration of general practice data using both the GPRD and the THIN databases. Whilst undoubtedly is it the older population with venous leg ulceration that has the major share of the burden of leg ulceration, younger adults are not immune from developing this condition. A large data source is required to examine the epidemiology of leg ulcers. This is to ensure that accurate estimates of leg ulcer burden in both younger populations and of rarer pathologies such as arterial and mixed venous arterial leg ulceration can be obtained. Furthermore, these databases allow the calculation of rates by any age specific category required. This means that the data can be directly standardised to any standard population required. By calculating standardised rates, comparison can be made between these databases, and the consistency of the results between them established. The aim of this study was to assess the similarity of incidence and prevalence estimates from two general practice databases.

3.2 Research Questions

1. What are the standardised estimates of incidence and prevalence of leg ulceration in the GPRD and THIN databases?
2. Do the GPRD and THIN databases provide consistent standardised estimates of the incidence and prevalence of leg ulceration?
3. Do the GPRD and THIN databases provide consistent estimates of leg ulcer duration?

3.2.1 Ethical approval

Ethical approval was sought to use both the GPRD and THIN databases. Approval to conduct the study using the GPRD was granted by the Independent Scientific and Advisory Committee of the GPRD. Approval to conduct the study using the THIN database was provided by the Cambridgeshire 4 Research Ethics Committee, reference number 08/H0305/21.

3.3 Methods

3.3.1 Case ascertainment

The first and potentially most important facet of designing a study using a clinical database is defining the 'caseness' of interest. For this study, the earlier work by Margolis et al. (2002) provided a starting point as a defined set of coding algorithms were used to identify patients with venous leg ulceration.

Following discussion with Dr Margolis, Professor Nicky Cullum and experts from the GPRD and THIN databases a list of Read and OXMIS codes was compiled to identify the cohort of patients with a database diagnosis of leg ulcers of venous, arterial and mixed venous arterial pathology. Patients with these differential diagnoses of leg ulcers were identified using the codes shown below in Table 3.1.

The two databases use different methods of coding to classify the '*caseness*' of patients. In the GPRD OXMIS, Read and GPRD medical codes are used, and in the THIN database only Read codes are used.

OXMIS codes

Oxford Medical Information Systems or OXMIS codes were, along with Read codes, the coding terminologies used the NHS in the 1980's. OXMIS codes were loosely based on the eighth revision of the International Classification of Diseases(ICD-8) and were designed to give a wide choice of codes for the same condition ensuring that a code matching the GP's diagnosis was available (GPRD 2007).

Read codes

Read Codes were first developed for private use by Dr James Read. Following widespread endorsement, the codes were purchased by the NHS and were formally introduced into the NHS and general practice in 1994, replacing the use of OXMIS codes (GPRD 2007). Read codes are a clinical coding system that allows for the coding of diagnoses and procedures. The classification also includes codes for symptoms, test results, screening, family history and many other areas (Primary Care Electronic Library 2010).

GPRD medical codes

The GPRD has its own system of unique codes creating a harmonised coding system integrating all coding systems used in the GPRD be they OXMIS or Read codes. Where possible, the same codes were used to identify prevalent and incident leg ulcer cohorts in the GPRD and the THIN databases. However, one of the older coding systems, OXMIS, was not used by the THIN

database. This resulted in 16 codes used by the GPRD that could not be used to identify patients in the THIN database. Of these 16 codes, 14 were used to code venous leg ulceration and two to code arterial leg ulceration. Table 3.1 below shows the codes that were used to identify leg ulcer patients from the GPRD and THIN databases.

It should be noted that not all clinical encounters will be recorded in primary care databases. Clinical and prescription events are recorded if they represent a new case of a condition or a first prescription, repeat prescription event or when a change of prescription or clinical diagnoses is given. Repeat visits for a chronic clinical condition that has been diagnosed but does not result in a change of management will not be recorded(Hansell et al. 1999).

Table 3.1 Comparison of codes used to identify the leg ulcer cohort in both the GPRD and THIN databases

GPRD Medical Code	Read / OXMIS Code	Read / OXMIS Term	Used in the THIN database	Diagnostic grouping
216082	G830.00	Varicose veins of the leg with ulcer	Yes	Venous leg ulcers
345418	G832.00	Varicose veins of the leg with ulcer and eczema	Yes	
339862	G837.00	Venous ulcer of leg	Yes	
339887	14F5.00	H/O: venous leg ulcer	No, OXMIS code	
219441	K914 RR	EXCISION VARICOSE ULCER	No, OXMIS code	
271667	M271500	Venous ulcer of leg	Yes	
303889	4540	VARICOSE ULCER LEG	No, OXMIS code	
303890	4540N	VARICOSE ULCER	No, OXMIS code	
303892	4540NE	VENOUS ULCER	No, OXMIS code	
280021	G832.00	Varicose veins of the leg with ulcer and eczema	Yes	
303891	4540NA	ULCER STASIS VARICOSE	No, OXMIS code	
289131	G835.00	Infected varicose ulcer	Yes	
256627	4540A	ULCER VARICOSE INFECTED (LEG)	No, OXMIS code	
262397	M271.00	Non-pressure ulcer lower limb	Yes	
256936	707 GL	ULCER LOWER LEG	No, OXMIS code	
235019	M271.13	Leg ulcer NOS	Yes	
304723	707 G	ULCER LEG	No, OXMIS code	
304724	707 GA	ULCER ANKLE	No, OXMIS code	
304718	707 AC	ULCER SKIN	No, OXMIS code	
256937	707L	ULCER GRAVITATIONAL CHRONIC	No, OXMIS code	
256935	707 AL	ULCER LOWER EXTREMITY	No, OXMIS code	
304719	707 A	ULCER SKIN CHRONIC	No, OXMIS code	
229574	707 AA	LEG ULCER ARTERIAL	No, OXMIS code	Arterial leg ulcers
262400	M271300	Arterial leg ulcer	Yes	
244012	M271.12	Ischaemic leg ulcer	Yes	
304721	707 AK	ULCER LEG ISCHAEMIC	No, OXMIS code	
253183	M271400	Mixed venous and arterial leg ulcer	Yes	Mixed venous/arterial leg ulcers

3.3.2 Introduction to GPRD and THIN data structures

The general practices that contribute patient data to both the GPRD and THIN databases can be thought of as an open cohort. Practices may contribute data for any length of time they wish and may subsequently stop contributing data. There are a number of variables that warrant discussion prior to reporting the methods used to undertake this study.

The two date variables recorded for each patient that are most useful to researchers in the GPRD are *regstart* and *regend*. The first of these variables, *regstart,* refers to the date when data were first collected for each patient and met GPRD quality standards. The second date, *regend,* refers to the date at which the practice stopped collecting data for the patient. Data collection may have ceased for a number of reasons including death of the patient, the patient no longer being seen in that practice or the practice ceasing to contribute data to the GPRD. The variable used to define the time point when practices met the GPRD definition of providing research quality data are also listed as the *UTS* or up to standard date. This date is equivalent to the date given in *regstart*.

Slightly different date and quality variables are used by THIN database. The three variables that are roughly equivalent to those used by the GPRD are *regdate, last collection date* and the *AMR date*. The first of these variables, *regdate,* refers to the date when data were first collected for each patient when they first registered with a practice that contributed to the THIN database. The second date, *last collection,* refers to the date at which the practice last contributed data to the THIN database. In common with regend used by the GPRD, it may have been due to patient or practice factors that data was no longer provided. The third date, the *AMR date*, denotes the year from which the practice is deemed to be accurately reporting all-cause mortality based on predicted numbers of deaths derived from national statistics taking into account the practice age and sex distribution (The Health Improvement Network 2007). The *AMR date* is not necessarily the same as the *regdate* as a practice may have met acceptable mortality reporting standards prior to or subsequent to a patients' registration date.

Although data entered in the GPRD and THIN databases are largely prospective, some retrospective data were also included. These data are introduced when practitioners record details of patients' historical medical conditions. The first time that a patient consults a practitioner with a specific medical condition is recorded in the GPRD database as an *index date*. The particular *index date* may have occurred many decades prior to registration with the current practice if it refers to a historical condition. As such the date chosen may be subject to recall error having been chosen based on the year that the patient first remembered the event occurring and may not be the actual date of occurrence. As the exact date of occurrence may be unknown, the date recorded in the database is usually although not always set at the first of January of that year. The

index date may also be entered prospectively if the patient is currently consulting with a new episode of a medical condition during their current registration. To ensure that only prospective data were included in the study it was imperative to ensure that the index date of a leg ulcer consultation had occurred subsequent to the patients' date of registration with the practice.

In the THIN database no field equivalent to the index date in the GPRD was created to denote the first occurrence of a leg ulcer in the database. All leg ulcer events were recorded as event dates. It is up to the researcher using the data to derive the first date of interest. To ensure that this date refers to a prospectively recorded episode of leg ulceration it is imperative that this date met two criteria to be consistent with the criteria applied to the GPRD data. First, that it occurred post the date of registration. Second, that it occurred after the date that the practice met the AMR quality standard.

3.3.3 Inclusion criteria

To minimise the potential for recall error and to ensure that all analyses were performed using high quality information, only prospectively collected data meeting the quality standard of the GPRD or the AMR of the THIN database were used. Therefore all data used for analyses in this study met the following two criteria;

i) the date of incidence or prevalence was recorded in the database between the dates of January 1988 and December 2006 ***and***

ii) the date that the patient was recorded as an incident or prevalent case was recorded within the date range when the data met quality standards and prior to end of a patients registration. These same criteria were also applied to the denominators for the calculation of incidence and prevalence ***and***

iii) that all data came from patients aged 20 years or greater on the date that criteria i) and ii) were met.

3.3.4 Additional inclusion criteria for the calculation of incidence

Additionally for the incident cohort, the inclusion criteria used by Margolis et al. (2002) were applied whereby cases were only considered incident if the following two criteria were met;

i) the initial diagnosis of leg ulceration was made at least six months after the commencement of the patient's database record ***and***

(ii) there was no diagnosis of any other form of leg or foot ulcer recorded in the three months after the initial diagnosis.

3.3.5 Method for calculation of average annual incidence density

Annual incidence density over the entire study period was calculated using the formula

$$\frac{\text{Number of new cases for each year between 1988 and 2006}}{\text{Number of person years at risk for each year between 1988 to 2006}}$$

Person-time was calculated to this studies specification by both the GPRD and THIN database administrators using the same methods previously used by Margolis et al. (2002). The starting time was defined as 6 months after the patient's first office visit and the end time as their last database record or the end of the study period if the patient was still registered with a GPRD practice. Additionally patients' data only contributed to the denominator if it met the same conditions as the numerator: i.e. data were contributed at a time when the practice met the GPRD requirement of being up to standard, or the THIN standard of meeting acceptable mortality reporting standards and the patient was aged 20 years or greater.

Crude annual incidence density rates were calculated for each year of the study period. Separate analyses were performed for all three forms of leg ulceration examined. These crude rates were presented per 100,000 person years.

3.3.6 Methods for the calculation of average annual period prevalence

Prevalence was calculated by including all patients aged 20 years and over, diagnosed with a leg ulcer who had made at least one visit to their general practice clinic in a given year (a baseline ulcer free-period was not required).

Annual period prevalence was calculated using the formula;

$$\frac{\text{Annual cases of leg ulceration for each year between 1988 and 2006}}{\text{Annual population at risk for each year between 1988 and 2006}}$$

Crude annual period prevalence rates were reported separately for each of the three diagnoses of leg ulceration examined. These results were presented per 100,000 persons at risk.

3.3.7 Methods for the calculation of standardised incidence and prevalence rates.

The results of crude incidence and prevalence from both databases were then standardised to the European standard population (Waterhouse et al. 1976). Standardisation was performed to remove any potential differences between the rates that were caused by the different age and gender distributions of the two databases.

The structure of the European standard population is shown below in Table 3.2.

Table 3.2 Age distribution of the European standard population

Age group	European Standard population
0	1,600
1-4	6,400
5-9	7,000
10-14	7,000
15-19	7,000
20-24	7,000
25-29	7,000
30-34	7,000
35-39	7,000
40-44	7,000
45-49	7,000
50-54	7,000
55-59	6,000
60-64	5,000
65-69	4,000
70-74	3,000
75-79	2,000
80-84	1,000
85+	1,000
Total	100,000

The European standard population used was the same whether rates are calculated for males, females or the genders combined. In this analysis age standardised rates were calculated for the total population of persons with leg ulcers in the population aged 20 years and over. It has been suggested that direct standardisation may not produce stable estimates if there are only small numbers of events available for analysis (Daly &Bourke 2000). In this study this was defined as less than 30 cases in any particular year. Direct standardisation of rates was not performed if this was the case for any database diagnosis of leg ulceration examined.

Confidence intervals and standard errors for the estimates of directly standardised rates were calculated using a normal approximation method as described by Breslow & Day (1987).
The formula used to calculate the upper and lower 95% confidence intervals for a rate in year a is given by:

$$\text{Rate}_a \pm (1.96 \times (s.e.\text{Rate}_a))$$

where $s.e.\text{Rate}_a$ is the standard error of the rate in year a.

The $s.e.\text{Rate}_a$ is derived as follows: $s.e.(\lambda_a) = \sqrt{\sum_{j-1}^{J} \frac{w^2_{ja} d_{ja}}{n^2_{ja}}}$

where w_j is the European Standard Population in age group j, d_{ja} is the number of occurrences in age group j in year a, and n_{ja} is the relevant population in age group j in year a.

The age specific rates of incidence and prevalence were then multiplied by the age specific population for that age category. These were calculated separately for incidence and prevalence, and by leg ulcer pathology.

Consider an example where the annual incidence density rate of venous leg ulceration in 1991 for persons aged 20-24 years was 63 per 100,000 person years. This age specific rate would then be multiplied by 7,000 as this is the European standard population for the age group 20 to 24 years. This then gives the number of patients as 441,000, that is the number of patients aged 20 to 24 years that would be expected to have a venous leg ulcer in a population with the same age distribution as the European population. These same values were then calculated for each age category in that same year. These values were then summed to produce total expected value for each year. These total expected values were then divided by 71,000, as this was the sum of the total European standard population aged 20 years and over. This results in the annual standardised rate.

The standardised rates calculated from both the GPRD and THIN databases were compared statistically by calculating a directly standardised rate ratio (SRR). In these analyses the SRR was the ratio between the standardised rates in the GPRD divided by the standardised rate from the THIN database. The formula used to calculate these ratios and their corresponding confidence intervals is as follows (Miettinen 1972);

$$(P1/P2)^{1\pm 1.96/\Phi}$$

$$\text{Where } \Phi=(P1-P2)/\sqrt{SE_1^2 + SE_2^2}$$

P1 and P2 represent the standardised rates from the two databases whilst SE_1 and SE_2 represent the standard error of the estimates from each of the two databases. The rates from the two databases were considered to be statistically significantly different if the 95% confidence interval of the SRR excludes one. A value of one indicates that the rates were equivalent.

Separate analyses were conducted for the results of both incidence and prevalence, and by database diagnoses of leg ulceration.

3.3.8 Methods for the calculation of leg ulcer duration

Leg ulcer duration was calculated as the elapsed time in days between the date of the incident database record of leg ulceration and the final database record of leg ulceration within the study period of January 1988 to December 2006. Results of mean and median duration were presented separately for each database diagnosis of leg ulceration.

3.4 Results

3.4.1 Results of incidence

The records of patients that met the criteria as an incident case were extracted from the two primary care databases and examined.

GPRD results

The original data set supplied by the GPRD contained the records of 61,068 patients with a database diagnosis of leg ulceration. Of these patients, 36,260 or 59% met the inclusion criteria as an incident case during the study period of January 1988 to December 2006 and were considered for further analysis.

THIN results

The dataset supplied by the THIN database contained the records of over 22,788 patients with a database diagnosis of any form of leg ulceration. Of these patients 20,261 or 89% met the inclusion criteria as an incident case over the same study period and were included for further analysis.

3.4.2 Summary characteristics of incident cohort

The baseline characteristics of incident leg ulcer patients identified in the two databases are shown below in table 3.3. The results are presented stratified by the database diagnosis of leg ulceration and database.

Table 3.3 Baseline characteristics of the incident cohort

	GPRD	THIN
Ulcer type, N(%)		
Venous	37575 (98.2)*	19378 (96.0)*
Arterial	523 (1.4)+	599 (3.0)*
Mixed	138 (0.4)^	284 (1.0)^
Total	38236 (100)	20261 (100)
Patient characteristics		
Female N(%)	24,830 (65.0)	12870 (63.5)
Mean age (SD)	73.2 (14.4)	73.2 (14.1)
Median, range	76 (18-109)	76 (18-109)

* study period of 1988 to 2006
+ study period of 1989 to 2006
^ study period of 1996 to 2006

The investigation of incident venous leg ulceration and mixed venous arterial was conducted over the same time period in both databases. For incident venous leg ulcers, cases were recorded between 1988 and 2006. For mixed venous arterial leg ulceration, cases were recorded in the both

databases from 1996 to 2006. Differences were only apparent when incident cases of arterial leg ulcers were examined. Cases were found in the THIN database from 1988 onwards in contrast to the GPRD where cases were found from 1989 onwards.

The demographic characteristics of patients by diagnostic grouping showed little variation between the two databases. Venous leg ulceration was the most commonly encountered form of leg ulceration, followed by arterial and then mixed leg ulceration. This same result was observed in both databases. For all three leg ulcer diagnoses, a greater proportion of females developed the condition compared to males. More incident patients were diagnosed with non-venous leg ulcers in the THIN database compared to the GPRD (4% *vs* 1.8%).

The crude estimate of the incidence density rate of venous leg ulceration over the study period was 122 per 100,000 person years (95% C.I. 120.7-123.2) in the GPRD and 81 per 100,000 person years (95% C.I. 79.9-82.2) in the THIN database. The results of a comparison of crude annual incidence density rates of venous leg ulceration obtained from the GPRD and THIN databases was undertaken and is shown below in figure 3.3. Differences between the crude rates of the incidence density of venous leg ulceration that were evident early in the study period, were shown to diminish considerably from the year 2000 onwards.

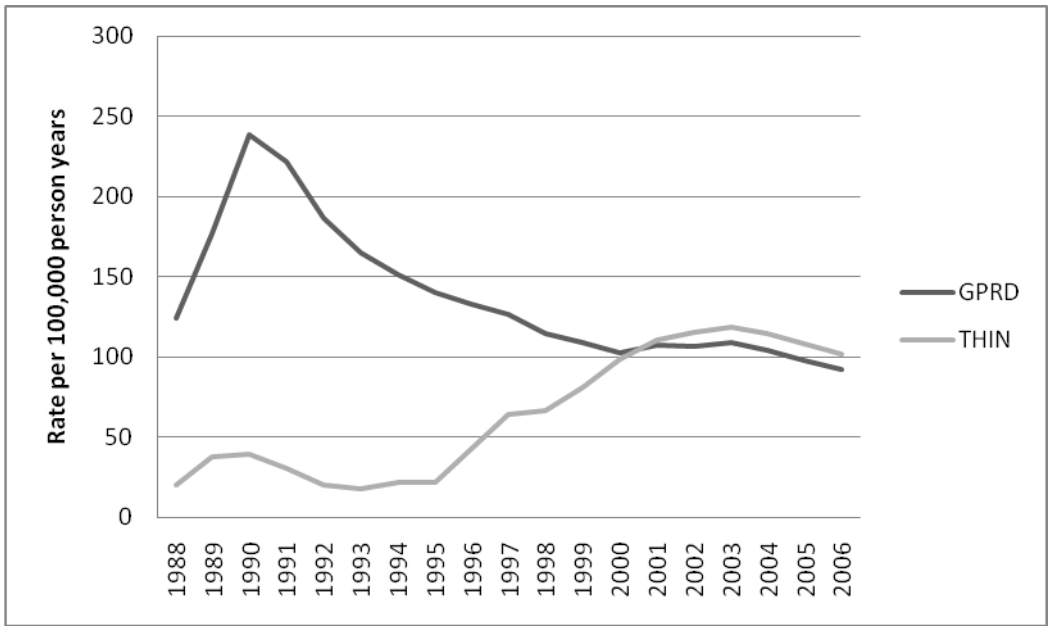

Figure 3.3 Comparison of crude estimates of annual venous leg ulcer incidence density from the GPRD and THIN databases

To further test whether rates from these two databases were comparable, the crude incidence density rates of venous leg ulceration obtained were standardised to the European standard population. These results are shown below in figure 3.4.

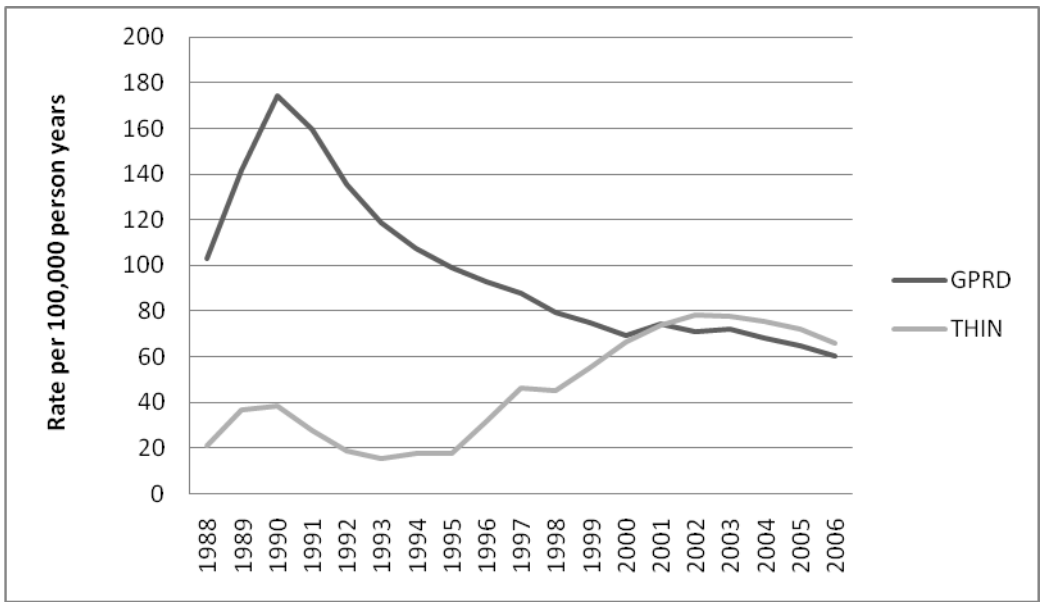

Figure 3.4 Comparison of estimates of age standardised annual venous leg ulcer incidence density from the GPRD and THIN databases

Standardised incidence rates were shown to follow a very similar temporal pattern to the crude rates although the actual estimates produced were lower. Once again, rates from the GPRD were shown to peak in 1990 whilst rates in the THIN database remained considerably lower until 2000.

Lastly standardised rate ratios (SRR) were calculated to statistically compare the standardised venous leg ulcer incidence density rates from the GPRD and THIN databases. This analysis was undertaken to determine if there were statistically significant differences in the standardised estimates. The result of this analysis is shown below in table 3.4.

Table 3.4 Comparison of standardised rate ratios of the annual incidence density of venous leg ulceration from the GPRD and THIN databases

Year	SRR	Lower CI	Upper CI
1988	4.93	4.36	5.49
1989	3.83	3.60	4.06
1990	4.54	4.45	4.63
1991	5.70	5.64	5.76
1992	7.29	7.23	7.35
1993	7.72	7.67	7.79
1994	6.11	6.04	6.17
1995	5.64	5.58	5.71
1996	2.94	2.85	3.03
1997	1.90	1.77	2.03
1998	1.74	1.60	1.89
1999	1.35	1.10	1.60
2000	1.04	-0.70	2.78
2001	1.01	-10.30	12.31
2002	0.91	0.26	1.56
2003	0.92	0.14	1.71
2004	0.90	0.29	1.52
2005	0.90	0.30	1.49
2006	0.91	0.21	1.60

SRR-Standardised rate ratios
CI-Confidence interval

Between the study years of 1988 and 1999, standardised rate ratios indicated that estimates of venous leg ulcer incidence obtained from the two databases were statistically significantly different. However from the year 2000 onwards statistical differences between the databases were no longer evident. The value one was obtained in the confidence intervals of the SRR for each year examined indicating that there were no statistically significant differences between the estimates obtained.

Next comparisons were made between estimates of crude and standardised rates of arterial leg ulcer incidence density from the GPRD and the THIN databases. In the GPRD results were available from 1989 to 2006 whilst in the THIN database results were available from 1992 to 2006. Overall, estimates of the crude incidence density of arterial leg ulceration varied between the databases. Rates of 2.51 per 100,000 persons were observed in GPRD (95% C.I. 2.31-2.71 per 10,000 person years) and 1.79 per 100,000 person years in the THIN database (95% C.I. 1.64-1.95 per 100,000 person years).

Shown below in figure 3.5 is the comparison of crude annual incidence density rates of arterial leg ulceration from each of the primary care databases.

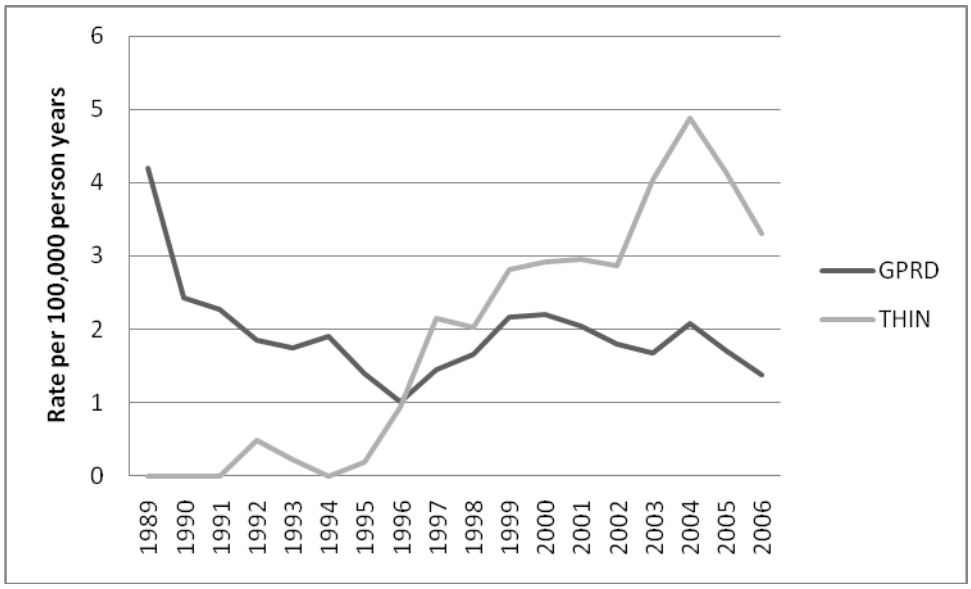

Figure 3.5 Comparison of estimates of crude annual arterial leg ulcer incidence density from the GPRD and THIN databases.

Although there were differences observed in crude rates of incident arterial leg ulceration obtained between the two databases, this difference was never more 3 people per 100,000 person years at risk between the years 1992 and 2006. Next the crude annual rates of incident arterial leg ulceration were standardised to the European population. This analysis can be seen below in figure 3.6. Standardised rates could only be compared between the two databases from 1997 onwards. Prior to 1997, the average number of prevalent patients identified annually averaged less than 20, as such any estimates produced would be unstable and were not reported.

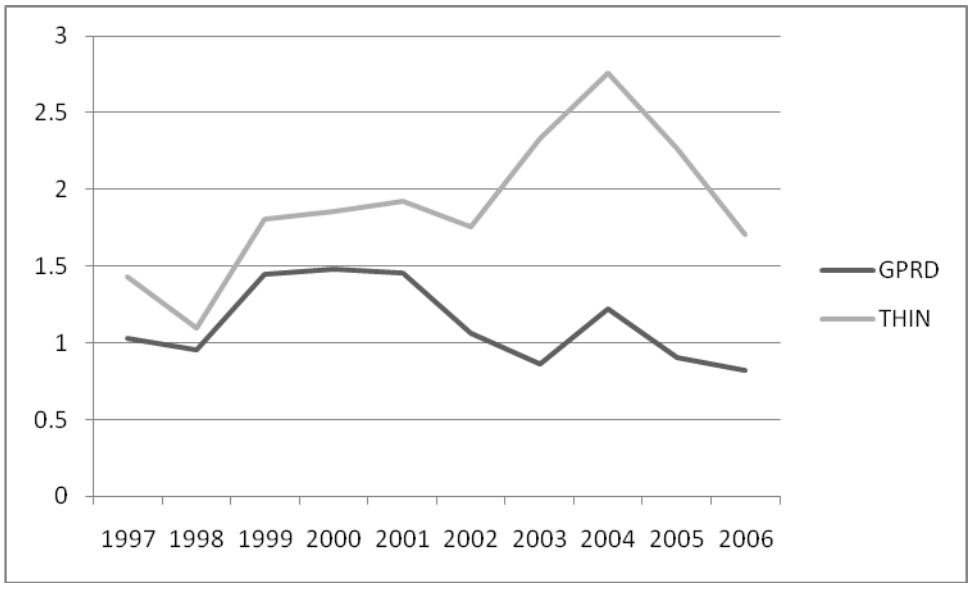

Figure 3.6 Comparison of estimates of age standardised annual arterial leg ulcer incidence density from the GPRD and THIN databases.

When the crude estimates of arterial incidence density were age standardised, differences in the rates between the databases grew ever smaller. These results are shown in table 3.5 below. There was never more than a 2.5 per 100,000 person year's difference in the standardised annual incidence density rates of arterial leg ulceration in the estimates produced by the two databases. There was some variation in the standardised rate ratios of arterial leg ulceration over the study period. During the years 1997 to 2002, and in 2006, no statistically significant differences between rates were observed. However, statistically significant differences in rates were observed over the period 2003 to 2005 although Negative lower confidence limits show that these confidence intervals are approximate and the large sample method does not apply well here.

Table 3.5 Comparison of standardised rate ratios of the annual incidence density of arterial leg ulceration from the GPRD and THIN databases

Year	SRR	SRR LCI	SRR UCI
1997	0.72	-1.11	2.55
1998	0.87	-3.20	4.93
1999	0.79	-1.31	2.91
2000	0.80	-1.16	2.75
2001	0.76	-0.79	2.31
2002	0.61	-0.30	1.50
2003	0.37	-0.07	0.81
2004	0.44	-0.03	0.91
2005	0.40	-0.06	0.86
2006	0.48	-0.14	1.11

SRR- Standardised rate ratio
CI-Confidence interval

The number of patients with a database diagnosis of incident mixed venous arterial leg ulceration did not exceed 20 patients in any study year in either database. These data were not standardised as the small numbers of these data means that any estimates produced were likely to be unstable.

3.4.3 Results of prevalence

To be included as a prevalent case, patients had to have a database record of a leg ulcer diagnosis occurring between January 1988 and December 2006 in either the GPRD or the THIN databases. A summary of the results of prevalence from each of the databases is provided below.

GPRD prevalence results

The original data set supplied by the GPRD contained the records of 61,068 patients with a database diagnosis of venous, arterial or mixed venous arterial leg ulceration. Of these patients, 48,887 or 80.1% met the inclusion criteria as a prevalent case during the study period of January 1988 to December 2006 and were considered for further analyses.

THIN prevalence results

The dataset supplied by the THIN database contained the records of over 22,788 patients with a database diagnosis of any form of leg ulceration. Of these patients, 21,861 or 95.9% met the inclusion criteria as a prevalent case during the study period and were included for further analyses.

3.4.4. Summary characteristics of the prevalent cohort

The baseline characteristics of the prevalent leg ulcer cohort identified in both databases are shown below in Table 3.6. The results are presented stratified by the database diagnosis of leg ulceration and database location.

Table 3.6 Baseline characteristics of the prevalent cohort

	GPRD	THIN
Ulcer type, N(%)		
Venous	47760 (97.7)*	20619 (94.3)*
Arterial	920 (1.9)+	810 (3.7)+
Mixed	207 (0.4)^	279 (2.0)^
Total	48887 (100)	21708 (100)
Patient characteristics		
Female N(%)	31,767 (65.0)	13336 (64.6)
Mean age (SD)	74.0 (14.3)	73.8 (14.2)
Median, range	77 (18-109)	77 (18-109)

* study period of 1988 to 2006, + study period of 1989 to 2006, ^ study period of 1996 to 2006

The characteristics of the prevalent cohort by database leg ulcer diagnosis were quite consistent in both databases. In common with the earlier results for incidence, most prevalent patients had a database diagnosis of venous leg ulceration and greater numbers of women had leg ulcers compared to men. However there were greater numbers of prevalent non-venous leg ulcer patients in the THIN database compared to the GPRD. The mean and median ages of prevalent cases were higher than those observed earlier for incident cases as would be expected with a chronic recurrent condition such as leg ulceration.

Crude annual prevalence rates of venous leg ulceration were calculated and the results between the databases compared. The result of this comparison is shown below in figure 3.7.

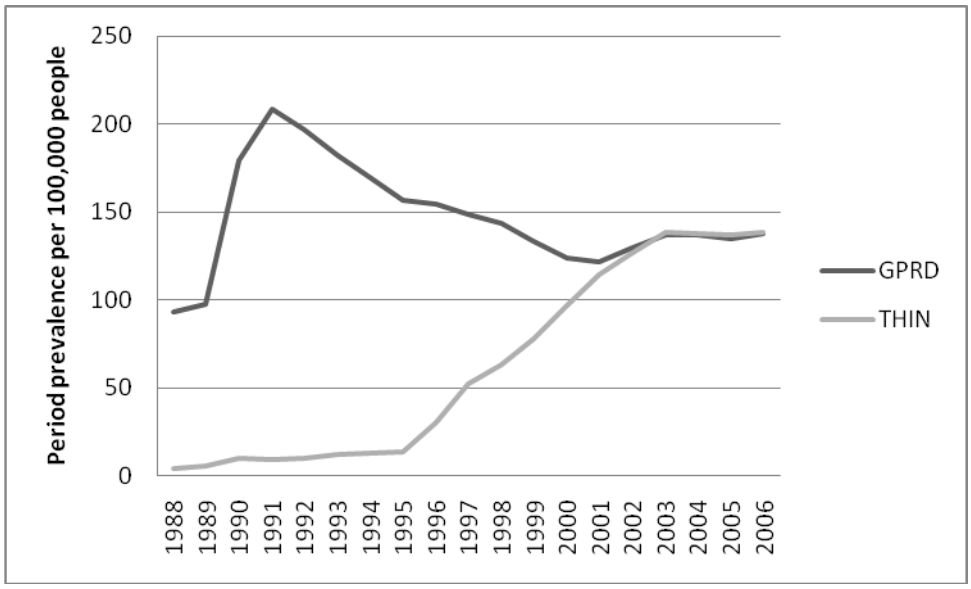

Figure 3.7 Comparison of estimates of crude annual venous leg ulcer period prevalence from the GPRD and THIN databases.

During the years 1988 through to 1999, crude annual prevalence rates of venous leg ulceration from the GPRD were higher than the crude annual rates from the THIN database. From 2000 until the end of the study period in 2006, crude annual rates between the two databases showed little variation. Rates over the entire period ranged from 82.8 per 100,000 person years in the THIN database (95% C.I. 81.7-83.9) to 140.7 per 100,000 person years in the GPRD (95% C.I 139.5-142.0).

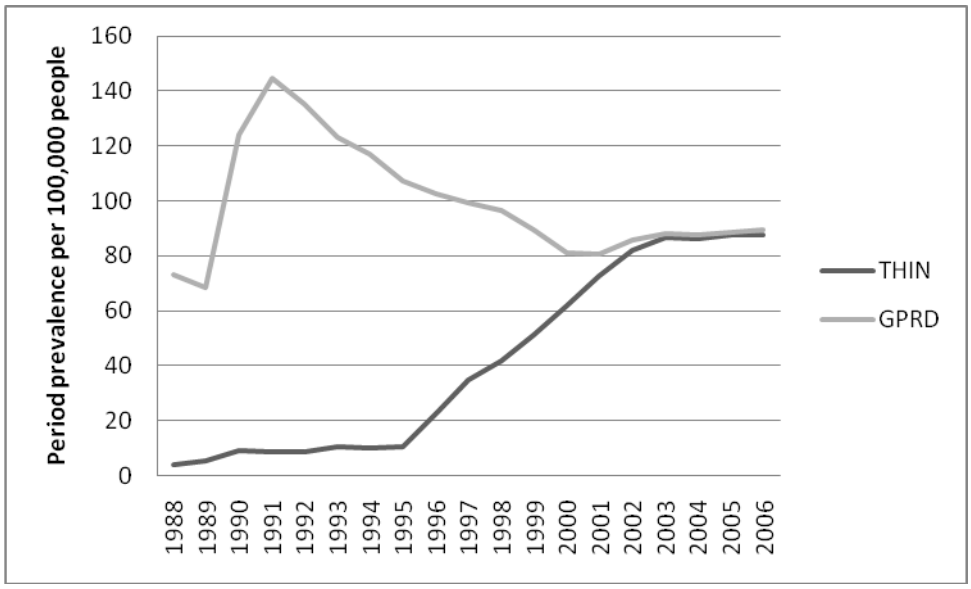

Figure 3.8 Comparison of estimates of standardised annual venous leg ulcer period prevalence from the GPRD and THIN databases.

Crude rates from both databases were standardised to the European standard population and the results of this analysis are shown above in figure 3.8. Standardised rates of venous leg ulcer

prevalence showed similar temporal patterns to the earlier crude results although the estimated rates were approximately half of the crude results. The results demonstrated that there were large differences in rates between the databases over the period 1988 to 1999. Standardised rates from 2000 onwards narrowed the results between the two databases further than the crude results. Results within the time period 2000 to 2006 were never than more than 20 per 100,000 persons different between the databases. By 2006 the difference between the results from both databases had once again narrowed to 2 per 100,000 persons.

Standardised rate ratios were calculated to examine any potential differences in the prevalence rates between the two primary care databases. The results of these analyses are shown below in table 3.7.

Table 3.7 Comparison of standardised rate ratios of the annual period prevalence of venous leg ulceration from the GPRD and THIN databases

Year	SRR	LCI	UCI
1988	18.29	18.00	18.58
1989	12.27	12.14	12.39
1990	13.91	13.85	13.97
1991	16.59	16.54	16.64
1992	15.75	15.70	15.80
1993	11.92	11.87	11.97
1994	11.43	11.38	11.49
1995	10.15	10.10	10.20
1996	4.56	4.50	4.63
1997	2.86	2.79	2.94
1998	2.32	2.22	2.41
1999	1.75	1.63	1.88
2000	1.31	1.07	1.55
2001	1.11	0.53	1.69
2002	1.04	-0.31	2.40
2003	1.02	-1.80	3.84
2004	1.01	-2.86	4.89
2005	1.01	-3.33	5.35
2006	1.02	-1.69	3.73

SRR- Standardised rate ratio
CI- Confidence interval

Standardised rate ratios of venous leg ulcer prevalence were statistically significantly different between the two databases from the beginning of the study period in 1988 until 2000. From 2001 onwards no differences were observed between the standardised estimates of venous leg ulcer prevalence from the two primary care databases.

Next, exploration of prevalent arterial leg ulceration was undertaken. The results of the comparison of crude rates between the GPRD and THIN databases are shown below in figure 3.9.

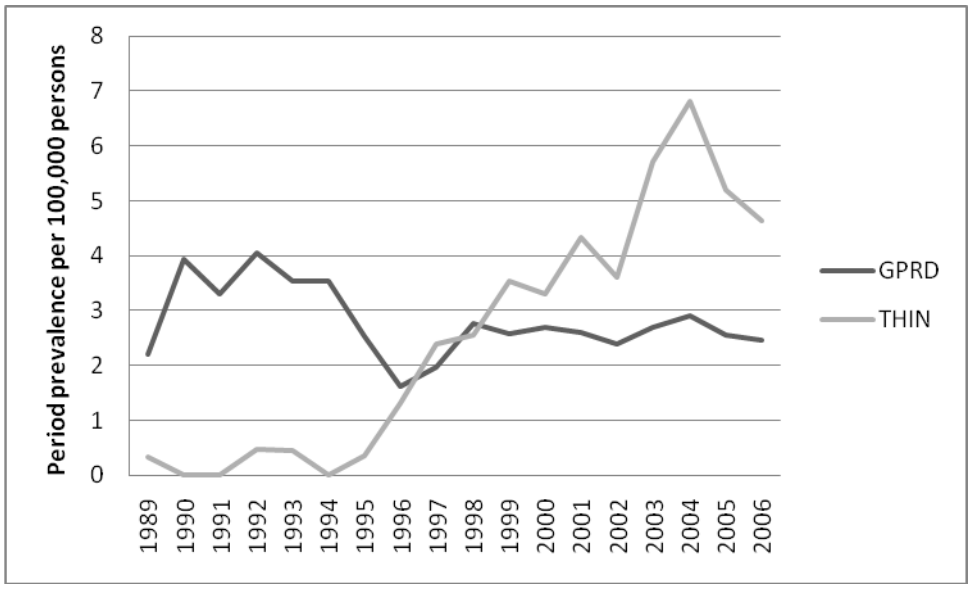

Figure 3.9 Comparison of estimates of crude annual arterial leg ulcer period prevalence from the GPRD and THIN databases.

Crude estimates of annual prevalence rates of arterial leg ulcers from the GPRD were relatively stable throughout the entire study period, with rates never varying by more than 3.5 per 100,000 persons. Greater instability was observed in the rates obtained from the THIN database where rates were shown to range from zero to 6.8 per 100,000 persons (95% C.I. -0.06-8.31) compared to the range of 1.6 to 4.1 per 100,000 person years in the GPRD (95% C.I. 1.5-5.33).

Next, the crude prevalence rates of arterial leg ulceration were standardised to the European standard population. These results are shown below in figure 3.10. Crude rates of arterial prevalence from the years 1997 to 2006 were standardised to the European standard population as there were sufficient numbers of cases per year. Prior to this year the number of prevalent cases of arterial leg ulcers in either databases averaged less than 30 per year. This means that the results of any standardisation performed would be unstable due to the small number of cases.

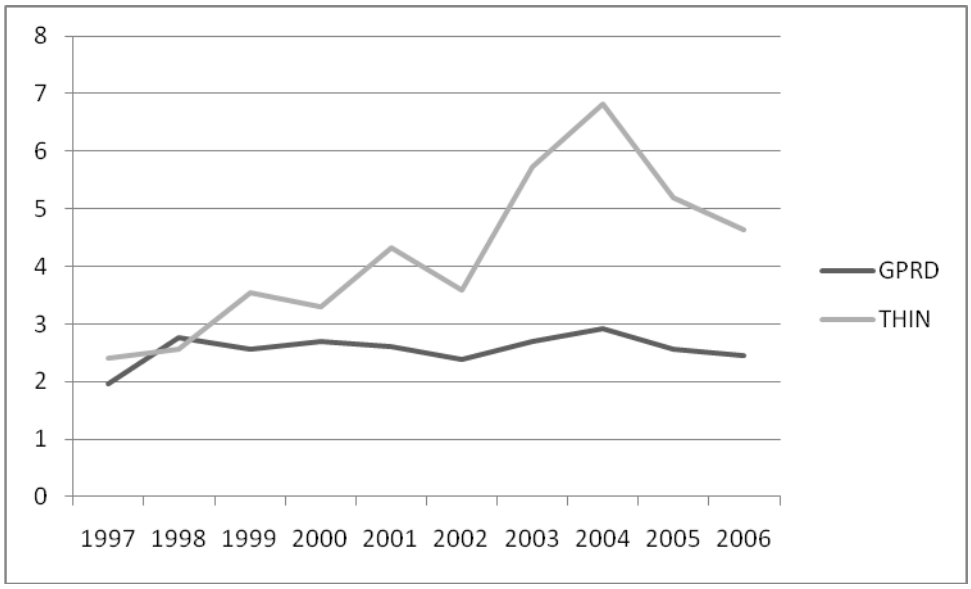

Figure 3.10 Comparison of estimates of standardised arterial leg ulcer annual period prevalence from the GPRD and THIN databases.

Next, these standardised estimates of arterial prevalence were compared statistically by calculating a standardised rate ratio and corresponding confidence intervals. These results are shown below in table 3.8.

Table 3.8 Comparison of standardised rate ratios of the annual period prevalence of arterial leg ulceration from the GPRD and THIN databases

Year	SRR	Lower CI	Upper CI
1997	0.84	-2.10	3.78
1998	1.19	-1.43	3.81
1999	0.80	-1.00	2.60
2000	0.98	-18.56	20.52
2001	0.68	-0.23	1.58
2002	0.67	-0.31	1.66
2003	0.48	0.02	0.94
2004	0.49	0.05	0.94
2005	0.48	-0.01	0.98
2006	0.62	-0.14	1.37

SRR- Standardised rate ratio
CI- Confidence interval

Standardised rate ratios of arterial leg ulcer prevalence indicated no statistically significantly differences existed between the two databases from the beginning of the comparison period in 1997 until 2002 and then again in 2006. Only between 2003 and 2005 were statistically significant differences observed between the standardised estimates of arterial prevalence obtained between the two databases.

3.4.5 Results of the exploration of leg ulcer duration

Duration of all three database diagnoses of leg ulceration in days was calculated and the results are shown below in table 3.9 for the GPRD and in table 3.10 for the results from the THIN database. The results indicated that the duration of the three forms of leg ulcers examined were highly skewed towards zero days. As such the mean values reported here must be interpreted with caution as these results are highly influenced by the few values of longer duration that were observed.

Table 3.9 Summary of leg ulcer duration stratified by database leg ulcer diagnosis from the GPRD

	Venous	Arterial	Mixed venous arterial
Mean (SD) days	180.5 (404.7)	206.7 (527.5)	285.9 (535.1)
Median, IQR days	0, 0-111	0, 0-130	13, 0-302
Range days	0-2542	0-3773	0-3259

Table 3.10 Summary of leg ulcer duration stratified by database leg ulcer diagnosis from the THIN database

	Venous	Arterial	Mixed venous arterial
Mean (SD) days	515.1 (1078.0)	56.1 (237.3)	111.5 (274.8)
Median, IQR days	0, 0-398	0, 0-2	13, 0-48
Range days	0-6570	0-2409	0-1481

Next the relationship between duration and gender was examined. Box plots of the stratified duration data are presented as the previous results had indicated that the results of duration are heavily negatively skewed. Shown below in figure 3.11 are the results of duration for venous leg ulceration, stratified by gender from both the GPRD and the THIN databases.

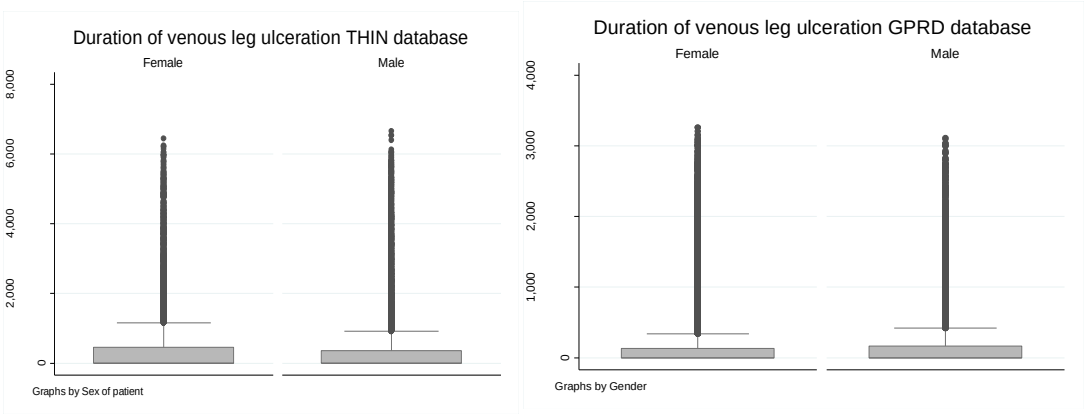

Figure 3.11 Duration of venous leg ulceration in the GPRD and THIN database

These results show that the median duration of venous leg ulceration in both the GPRD and THIN databases for both genders was zero days and therefore no gender relationship was

evident. However, the range of duration was greater in the THIN database ranging from zero to over 6,000 days, compared to a highest value of 3200 days obtained from the GPRD.

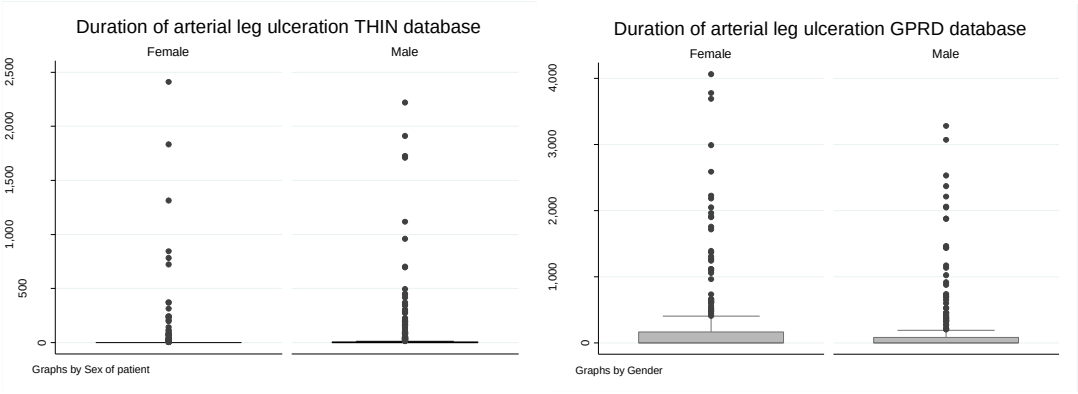

Figure 3.12 Duration of arterial leg ulceration in the GPRD and THIN database

The values for the duration of arterial leg ulceration, shown above in figure 3.12, were also shown to be centered around zero days and again showed no relationship with gender. Values did however indicate greater variation of duration in the GPRD compared to the THIN database.

Lastly, the duration of mixed venous arterial leg ulceration from the GPRD and THIN was examined. These results are shown below in figure 3.13

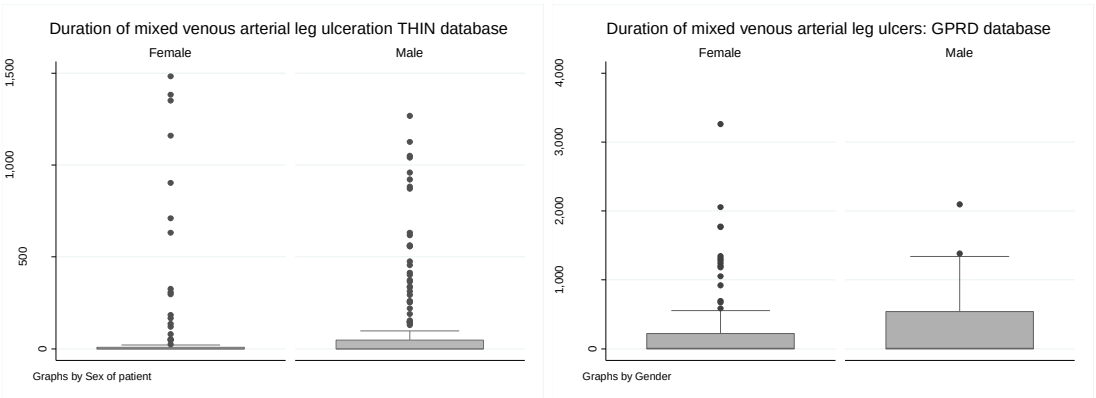

Figure 3.13 Duration of mixed venous arterial leg ulceration in the GPRD and THIN database

For mixed venous leg ulceration the median duration was found to be 13 days in both databases. Unlike the previous two diagnoses an association between male gender and longer duration of mixed venous leg ulceration was observed.

Although duration has been calculated, there is some concern regarding the validity and applicability of these results. The way in which chronic conditions are coded in primary care means that the values of duration obtained are likely to be underestimates. This is because visits for all clinical conditions are only entered into the database if they are for a new condition or when there has been a change in management. Therefore if treatment continues without change there will be no record of these visits.

3.5 Discussion

3.5.1 Statement of principal findings

Two large primary care databases were searched to identify leg ulcer patients with a database record of incident or prevalent venous, arterial or mixed venous arterial diagnoses consulting during the study period of January 1988 to December 2006. During this time period over 50,000 leg ulcer patients met the criteria as an incident case and over 60,000 met the criteria as a prevalent case. The majority of patients were found to have a database diagnosis of venous leg ulceration in both databases. Throughout the eighteen year period evaluated there were less than 1800 patients diagnosed with arterial leg ulceration and fewer than 650 patients diagnosed with mixed venous arterial leg ulceration.

Annual estimates of standardised venous leg ulcer incidence rates ranged from a low of 15.3 per 100,000 person years in the THIN database to a high of 174 per 100,000 person years in 1990 in the GPRD. Rate ratios suggested that from 2000 onwards there were no longer any statistically significant differences in rates between the databases with rates of approximately 60 per 100,000 person years observed in both databases. For arterial leg ulcers, annual standardised estimates of incidence ranged from 0.8 per 100,000 person years in the THIN database in 2006 to a high of 2.7 per 100, 000 person years in the GPRD in 2004. Despite these differences there were no significant differences between the annual rates of arterial leg ulcers between the years 2003 to 2005. These results indicated that comparable rates of both venous and arterial leg ulcers could be obtained from the GPRD and THIN databases.

For prevalence, standardised estimates of annual venous leg ulcer prevalence ranged from 4 per 100,000 people in 1988 in the THIN database to a high of 144 per 100,000 people in the GPRD in 1991. Rate ratios indicated that there were no statistically significant differences between the estimates produced between 2001 and 2006. Standardised estimates of arterial leg ulcers ranged from lows of 2.3 per 100,000 people in the GPRD and the THIN databases in 2002 and 1997 respectively. Whilst the highest rates of 6.8 per 100,000 people was observed in the THIN database in 2004. Standardised rate ratios showed that there were no differences between the rates obtained between databases in the years 2000 to 2002 and again in 2006.

These results show that there were statistically significant results between the databases for the majority of the eighteen year study period investigated, although these differences were shown to diminish from the year 2000 onwards. The exploration of leg ulcer disease burden trend over time should therefore be limited to these recent data to exclude the possibility of error caused by extrinsic differences in estimates of leg ulcer burden between the two databases.

Comparisons were not made between the estimates of either incident or prevalent mixed venous arterial leg ulceration due to the small number of patients with a record of this database diagnosis. Without a larger sample size, it is not possible to determine if the results of incidence or prevalence of mixed venous arterial leg ulceration obtained are comparable between the databases.

There are several reasons why there have been differences in leg ulcer burden of disease estimates between the GPRD and THIN databases. Irrespective of the primary care database that they contribute data to, practices that are newer are more likely provide incomplete data as they learn to use new computer systems and achieve new quality standards of clinical data reporting. During the study period investigated, more practices have joined the THIN database, including half of those that contribute to the GPRD. In contrast more practices have stopped contributing to the GPRD. By 2000, more of those practices that joined the THIN database had contributed data electronically for several years and had met the acceptable mortality reporting standard required by the database. These factors are the likely cause of the comparable estimates that have been observed in this study.

The duration all forms of leg ulceration was found to be low with the highest median duration observed being 13 days for mixed venous arterial leg ulcers. The coding method used means that only first time clinical events and clinical events which result in a change of management result in a database record (Hansell et al. 1999). The values obtained must be treated with caution as they are likely to be underestimates caused by the coding methodology employed in both databases as subsequent visits for chronic conditions are not coded unless there is a change in management.

3.5.2 Strengths and weaknesses of the current study

This study was undertaken using two of the largest general practice databases available in the UK containing longitudinal data to examine the comparability of leg ulcer disease burden trends over time. The current study used a previously validated case ascertainment strategy to identify patients with venous leg ulceration. This was found to be sufficiently sensitive and specific when identifying patients in the GPRD (Margolis et al. 2002). Although this study was limited as no leg

ulcer validation studies have been undertaken in the THIN database, it is known that approximately half of all practices that provide data to the GPRD also contribute to the THIN database (The Health Improvement Network 2007). A further limitation of this study is that the case ascertainment strategy used to identify arterial and mixed venous arterial leg ulcers has not been validated in either of the two primary care databases used and thus the accuracy of these database diagnoses remains unknown. There is the possibility that there may be misclassification of the database leg ulcer diagnosis.

There are several methodological advantages to using primary care databases to derive burden of disease estimates. First, this study was not subject to non-response bias that was evident in many earlier studies where case ascertainment was dependent upon surveying health professionals to identify leg ulcer patients (Graham et al. 2003a). In some studies fewer than 50% of health professionals responded to requests for details of their leg ulcer patient population (Hickie et al. 1998). Second, the methods used in the current study ensured that all results were based prospectively collected clinical data that had met stringent quality standards. Second, the strength of this approach means that data were not subject to recall error or selection bias from either patients or practitioners. Patients may find it difficult to remember when they were first diagnosed with leg ulceration or for how long they have had the condition, particularly due to the chronic recurrent nature of the condition. Recall error was therefore eliminated in the current study as the data obtained comes from prospectively collected primary care medical records. Selection bias is also excluded as all patients records can be accessed so there is no chance of any patient's records being systematically excluded.

Despite the large sample size of the databases, the number of patients with a database diagnosis of mixed venous arterial leg ulcers observed in this study was low. There are several reasons why this might be the case. First, the Read codes needed to record this aetiological event were not available for practitioners to use throughout the entire study period, only becoming available from 1996 onwards. Second, it is unclear what proportion of patients with mixed venous arterial leg ulcers may have been misclassified as having another diagnosis of leg ulceration. This is because no additional clinical validation of the database diagnosis results was performed. Given how rare this form of leg ulceration was shown to be, it was inappropriate to directly standardise this aetiology of leg ulceration and undertake comparisons between the results in both databases. Other methods of comparison exist for small rates, such as indirect standardisation, but were not undertaken as they do not allow for non-biased comparisons to be made between different populations and different time points.

A final limitation of this study has been the inability to use these general practice data to obtain accurate estimates of the duration of leg ulcers. Duration estimates may be possible where there is prescribing data that is homogenous for a particular clinical condition, e.g. salbutamol for the treatment of asthma. In this example, prescription of salbutamol could be used in conjunction with Read codes for asthma as a proxy measure to obtain accurate information regarding the duration of asthma in primary care. The information recorded will therefore not produce accurate or reliable estimates of duration for chronic conditions where there is not a homogenous prescribing strategy. The database records of prescriptions for leg ulcers patients were not examined in the current chapter, but will be examined in further chapters (four and five). The feasibility of using prescription data in addition to Read codes to derive more accurate estimates of the duration of leg ulceration will be examined in the next two chapters.

3.5.3 Strengths and weaknesses in relation to other work

The crude annual prevalence rates of venous leg ulceration calculated in this study, from both the GPRD and the THIN databases, are broadly similar to previous estimates from studies conducted in the general adult population (Graham et al. 2003a). The prevalence estimates obtained by Graham et al. were 1.1% of the population with open ulcers which is comparable to the 0.9 per 100 people estimate for venous leg ulcer obtained in the current study. Previous estimates of leg ulcer incidence and prevalence show considerable variation in the populations included and in the methods used. For example, higher estimates were observed in studies limited to older populations, rather than total populations, and studies calculating period prevalence which produced higher estimates than studies calculating point prevalence. An earlier incidence and prevalence study, undertaken by Margolis et al. (2002) to examine venous leg ulceration incidence and prevalence in the elderly using the GPRD, was conducted using data collected between 1988 and 1996. The results from this current study show that the time period over which Margolis et al. (2002) produced their results, corresponded with the highest rates observed over the entire study period of 1988 and 2006 of the current study. Additionally, this time period corresponded with the greatest differences between estimates obtained from the GPRD and THIN databases. No data exists that has examined differences in the patient profiles of practices between the GPRD and the THIN database or the two different versions of the GPRD. As such the contribution of differences in patient profiles to the rates observed cannot be excluded as an explanation for the differences in results obtained between THIN and GPRD databases, or differences in rates to those observed in the earlier work conducted by Margolis et al. (2002).

There are two pieces of evidence to suggest that the data from these primary care databases may be more reliable from the year 2000 onwards. First, it has been suggested that estimates of

incidence density over time should only be calculated over a time period when rates are constant (Bhopal 2002). From the results of this study it can be clearly demonstrated that reported rates were highly variable over the time period of the Margolis et al. (2002) study, violating the assumptions of the calculation of incidence density. Second, from 2000 onwards, both the GPRD and the THIN database produced comparable rates and stable rates meaning that the current study was able to produce valid and reliable incidence density estimates of both venous and arterial leg ulceration.

The comparison of estimates of incidence and prevalence from the current study with previously published estimates is limited as no previous leg ulcer burden studies have produced standardised estimates using the European standard population. Whilst the crude rates presented in these earlier studies are relevant to the populations in which they were undertaken, they cannot be compared with other estimates or be used to perform comparisons over time in the same geographic area.

The aetiological classification of leg ulceration used in this study came from the Read code assigned by the treating health professional to the diagnosis of leg ulceration. The degree to which device based testing or standardised assessments of leg ulcer patients was undertaken was not assessed in the current study. Other studies that performed clinical validation of underlying leg ulcer circulation, or other clinical assessments to classify the pathology of the leg ulcer, observed different distributions of leg ulcer aetiology than that observed in the current study. For example, Callam et al.(1988) examined a subset of leg ulcer patients identified in an earlier prevalence study and found that 76% of all leg ulcers assessed were venous in nature. Moffatt et al.(2004) found that only 43% of all leg ulcer patients assessed had leg ulcers of venous origin. The patient assessments performed are likely to have contributed to variations in aetiological leg ulcer distributions. Callam et al.(1988) reported that all patients were given a standardised assessment although insufficient detail was provided to determine whether this assessment included device based testing. In contrast Moffatt et al.(2004) found a smaller proportion of patients suffered from venous leg ulceration than Callam et al.(1988). Moffatt et al.(2004) examined all patients using a combination of clinical assessment and non-invasive vascular testing including Doppler and plethysmography. The results of these two studies demonstrate that the methods used to diagnose leg ulcer aetiology are likely to greatly influence the distribution of leg ulcer aetiology observed.

It is conceded that the proportion of patients diagnosed as having venous leg ulceration in this study may be an overestimate. Conversely, it may also be possible that the numbers of patients deemed to have arterial and mixed venous arterial leg ulceration may have been underestimated.

It should further be noted that although the case ascertainment strategy for venous leg ulceration was validated and found to be reliable (Margolis et al. 2002), several of the Read codes used were for leg ulcers not otherwise classified. Previous work has shown that there are wide variations in the coding of clinical data across a wide range of specialities and although this has not been specifically examined in patients diagnosed with leg ulcers (Gray et al. 2003; Stone et al. 2010).

The current study has been able to eliminate many potential causes of bias and error that were evident in earlier burden of disease studies of leg ulcers. This study accessed patients' retrospective medical records meaning that there was no selection, systematic reporting bias or recall error that may be present in studies that relied on health care professionals to provide details of leg ulcer patients and patients for estimates of leg ulcer duration.

3.5.4 Meaning of the study

This study has established that consistent and comparable estimates of venous and arterial leg ulcer burden can be obtained from both the GPRD and THIN databases from the year 2000 onwards for estimates of incidence and 2001 onwards for estimates of prevalence. Data from these time periods can therefore be used to gain a greater understanding of both the epidemiology and management of leg ulceration using these two primary care databases.

As there may be variations in the methods of assessing or diagnosing leg ulcers by practitioners contributing to these databases it is likely that there will be some degree of diagnostic misclassification of leg ulcer aetiology. Despite this there was no evidence of any systematic difference in the diagnostic misclassification between the two databases.

Direct standardisation of rates enhances the epidemiological understanding of leg ulceration in several ways. First, it removes bias introduced when there are different age structures between populations. For example, crude estimates of the rate of leg ulceration will be higher in populations that have a greater proportion of older people. Second, it allows for a comparison of rates over time and both between and within defined geographical areas. Third, it allows for direct comparison of leg ulcer burden of disease data with disease burden of other conditions. At a public health policy level this will assist decision makers needing to monitor resource implications caused by multiple health conditions affecting the same population and improve the ability to commission services in this area.

The results in this study indicate that general practice data will not produce accurate or reliable data on the duration of leg ulcers due to the underlying coding methods used. In chronic

conditions where homogenous prescribing strategies are employed accurate estimates of disease duration could be obtained.

4.0 Exploration of factors affecting the distribution and management of leg ulceration in general practice: a study using the GPRD.

4.1 Introduction

This chapter presents the second study that forms the thesis. In the previous chapter, data from the GPRD and THIN databases were shown to produce comparable estimates of venous and arterial incidence from 2000 onwards and from 2001 onwards for prevalence estimates of venous and arterial leg ulcers. In the current chapter I will use the GPRD to explore two specific aims. The first of these two aims is to explore whether gender, age and year are associated with the incidence and prevalence of leg ulcers. The second is to examine whether patient or practice characteristics are associated with management and referral decisions reported for leg ulcer patients.

4.2 Background

In previous epidemiological studies, researchers performed only a limited analysis of factors thought to influence the burden of leg ulceration. In the majority of cases analyses were descriptive in nature, limiting the inferences that can be drawn. In the analyses performed by Margolis et al. (2002) and in the exploration of prevalence studies undertaken by Graham et al. (2003a) attempts were made to examine the confounding effect of variables such as age and gender on observed rates by stratifying estimates. Whilst stratification is a useful technique for preliminary examination of the effect of potential explanatory variables on rates, it may lead to biased findings as the technique does not allow for the simultaneous adjustment of multiple variables.

Given the limited exploration of the effect of variables on rates of leg ulcers there is potential for further analyses. To date studies that have performed stratified analysis have been restricted to examination of rates of venous leg ulceration or of all leg ulcers combined. The effect of age and gender on rates of arterial and mixed leg ulceration remains largely unexplored. There are statistical techniques available, such as Poisson regression, which will allow exploration of the independent relationships of multiple variables with rates.

The GPRD has been widely used as a data source to explore the management of a range of conditions in primary care; including asthma, depression and arthritis (Edwards et al. 2007; Turner et al. 2009; Watson et al. 2009). To date I have identified no publications that used the GPRD to examine the management of leg ulcer patients. This is despite the earlier work undertaken by Margolis et al.(2002) that examined venous leg ulcer incidence and prevalence in

the population aged greater than 65 years during the years 1988 to 1996. Several UK based guidelines for the management of leg ulceration were produced in the late 1990's but the extent of their implementation in routine clinical management in primary care has not been examined. The prospectively collected data from the GPRD provides an ideal opportunity to examine temporal changes in leg ulcer management that may have occurred since the introduction of these three leg ulcer guidelines.

Studies exploring the management of leg ulcers have typically examined two main aspects of care. First, there were studies that evaluated of the management of leg ulceration by primary care providers. These studies have typically surveyed health professionals and asked them to report on how they managed leg ulcer patients in their care (Hickie et al. 1998; Schofield et al. 2000; Graham et al. 2003b). Frequently there was no validation of the responses received, and the response rates were also poor. It is hypothesised that health professionals responding to such requests for information are likely to be those with a greater interest in leg ulcer care thus the results from these studies may not represent usual clinical practice. Second, other literature has examined the provision of specialist leg ulcer services such as nurse led leg ulcer clinics (Moffatt et al. 1992; Harrison et al. 2008). There is no evidence that specialist leg ulcer clinics represent typical leg ulcer management nationally. Furthermore, there is no evidence to suggest that specialist leg ulcer clinics result in better patient outcomes than other modes of leg ulcer service delivery (Thurlby &Griffiths 2002; Harrison et al. 2008).

The use of primary care databases to investigate the management of leg ulcers has the potential to overcome many of the shortcomings of previous work. First, by using primary care databases, researchers can access details of actual rather than self reported clinical practice from a nationally representative and validated source of primary care data with a large sample of leg ulcer patients. Second, the patient management information obtained is not subject to either non-responder or recall bias, as data are obtained prospectively from all contributing practices undertaking management of leg ulcer patients. Third, the analysis of data can move beyond descriptive analysis due to the large number of practices contributing data. This allows analysis to be undertaken and the effect of multiple variables on patient management using more robust methods such as regression analyses.

The GPRD contains variables at both the individual and the practice level, allowing the exploration of a range of variables hypothesised to be associated with leg ulcer development and management. Individual level variables examined in models include age, sex and study year. These variables were included as there was evidence to suggest that they would be likely to

influence both burden of disease and patient management and they were available in the database. The evidence for the inclusion of each of the variables will be discussed below in turn.

Age and gender

Previous research has consistently shown that older age and female gender are positively associated with higher rates of incident and prevalent leg ulcers (Margolis et al. 2002; Graham et al. 2003a). Despite this, no studies were found that examined the relationship between gender or age and the management of leg ulceration. In other diseases, studies have clearly shown that variations in care can occur for patients of different ages and genders. A recent study found that there were differences in prescriptions and hospitalisations between men and women for a range of conditions including diabetes, asthma and coronary artery disease (Stock et al. 2008). These gender inequalities in management were observed even when the results were controlled for age and co-morbidities of the patients (Stock et al. 2008). The inclusion of patient age and gender into models of leg ulcer management will allow any variations in care to be indentified.

Year

Year of diagnosis was included in analyses as practice may have varied over time, and it is important to adjust any results for temporal variations should they be found to exist. Three clinical guidelines were first introduced in 1998 and it is likely that these may have influenced changes in management in the preceding years (CREST 1998; SIGN 1998; RCN 2006). The inclusion of year of diagnosis into models will allow quantification of temporal patterns of disease burden and management.

Practice level deprivation

The practice level variable that will be examined in models examining leg ulcer management is a measure of practice level deprivation, the Index of Multiple Deprivation (IMD, 2004) (Noble et al. 2004). IMD (2004) of the practice was chosen for inclusion in the model as previous work has suggested that there are negative associations between higher levels of practice level deprivation and the quality of care provided to patients (Saxena et al. 2007). Practice level deprivation was only available for the numerator of leg ulcer patients only. Therefore, the effect of practice level deprivation on rates of leg ulceration could not be examined.

It is proposed that the results of this chapter will contribute to new knowledge in three main ways. First, the study will provide epidemiological data on the populations most likely to develop leg ulcers. This will enable policy makers to target resources to populations with the greatest need. Second, the data obtained can be used to determine whether there are any key aspects of management that may be suboptimal. Third, this analysis will allow exploration and identification

of any patient or practice level factors that may contribute to variations from guideline based recommendations of leg ulcer care.

4.3 Research Questions

1. Is there a relationship between age, gender or study and the annual incidence density or annual period prevalence rates of leg ulcers in persons aged 18 years or greater?

2. Which diagnostic tests, treatments and referral decisions are recorded as being used for the initial management of leg ulceration in UK general practice?

3. Does the reported diagnosis, initial management and referral of leg ulcer patients vary by patient or practice level variables?

4.4 Methods

In the previous chapter, the consistency of leg ulceration incidence and prevalence estimates from the GPRD and THIN databases were explored. The results of this analysis suggested that the two databases produced comparable estimates of venous and arterial annual incidence density from the 2000 to 2006. For the annual period prevalence of both venous and arterial leg ulceration, data from 2001 to 2006 was shown to be the most comparable. The numbers of patients diagnosed with mixed leg ulceration was too small to permit standardised analysis and thus a comparison of rates between the two primary care databases could not be reliably conducted.

It was therefore decided to restrict the analysis exploring the association of age, study year and gender and incidence density of leg ulceration, to data collected from 2000 to 2006. For the examination of prevalence, analyses were restricted to data collected from 2001 to 2006. For consistency, the same dates were chosen irrespective of the database diagnoses of leg ulceration examined. The full methods used to both identify and calculate the incidence and prevalence of leg ulcers of venous, arterial and mixed ulceration can be found in the previous chapter in section 3.3.

4.4.1 Methods for the exploration of the association of variables with incidence and prevalence rates

The relationship of age and gender with incidence and prevalence rates was first examined descriptively using graphs, with age examined in ten year categories from age 18 onwards. Separate graphs were produced for each of the diagnoses examined; venous, arterial and mixed

venous arterial. As there were very few patients aged greater than 98 years, these graphs were restricted to the results of all persons between the ages of 18 to 98 years.

Next, Poisson regression analyses were used to model the effect of multiple explanatory variables on rates of incidence and prevalence. The variables selected for inclusion in the models were age, gender and study year. For the regression analyses, the variable patient age was included in models with no upper age limit applied. The inclusion of study year into the models allowed exploration of the temporal patterns of incidence and prevalence. Furthermore, these three variables were chosen for inclusion in regression models as they were available for both the denominator and numerator of the rates and therefore could be examined using these methods.

Likelihood ratio tests were first used to examine any deviations from the Poisson distribution ensuring that appropriate regression models were undertaken relative to the underlying distribution of the data. If there was evidence of over-dispersion of nonzero counts relative to the Poisson distribution, a negative binomial regression approach was employed (Byers et al. 2003). Models were then estimated to examine the relationship between variables and incidence and prevalence rates separately for leg ulcers of all three database diagnoses of leg ulcers examined; venous, arterial and mixed venous arterial.

To aid in the interpretation of the co-efficients produced by these models, the results were expressed as either incidence rate ratios or prevalence rate ratios. Incidence rate ratios or prevalence rate ratios correspond to the exponential of the point estimate for the explanatory variable produced by the Poisson or negative binomial model. As an example, when the effect of gender on incidence rates was examined, the incidence rate ratio calculated referred to the difference in risk of leg ulceration of a woman compared with a man. Thus, these estimates can be conceptualised in a similar way to a risk ratio. The results of all analysis presented are adjusted rate ratios as the co-efficients presented are those produced when all explanatory variables were included in the model.

The results of all statistical tests were assumed to be statistically significant when the value was less than or equal to 0.05. Confidence intervals for the estimates of incidence rate ratios or prevalence rate ratios were also reported and indicated a statistically significant result if they did not include the value one.

4.4.2 Methods for the exploration of initial ulcer assessment

The three UK based guidelines for the management of leg ulceration all concluded that the initial clinical assessment of leg ulcer patients should include the use of Doppler ultrasound to aid

calculation of the ABPI (CREST 1998; SIGN 1998; RCN 2006). To undertake the measurement of the ABPI, a Doppler ultrasound is used as an aid to blood pressure measurement in both the arm and in the ankle. Blood pressure measurements are recorded at the point that the pulse sounds reappear after the cuff is deflated, shown below in figure 4.1. The ratio between these two measures is then calculated to produce the ABPI.

Figure 4.1 Hand held Doppler probe on dorsalis pedis. (From McPherson and Wolfe)

It is recommended that the ABPI be used in conjunction with other clinical signs and symptoms to exclude the presence of significant peripheral vascular or arterial disease and guide appropriate management (RCN 2006). Ratio values below 0.8 represent a contraindication for compression bandaging due to the presence of arterial disease (RCN 2006) as well as being an independent predictor of mortality (Leng et al. 1996; Jönsson &Skau 2002). The use of ABPI measurement provides a useful adjunct diagnostic method to aid clinical decision making for the management of leg ulcer patients.

An inclusive approach was undertaken when examining the reported use of Doppler ultrasound as part of the diagnostic assessment of leg ulcer patients. First, database records in the 30 days prior to a patient's incident diagnosis were searched for a record of an ABPI measurement, it being conceivable that measurements were made prior to the record of incident leg ulcer diagnosis. Next records were checked for codes indicative of ABPI measurement in the 90 days post diagnosis. Ninety days post diagnosis was chosen as Margolis et al. (2002) suggested that '*three months is a reasonable length of time to allow for a complete evaluation and diagnosis of a person with a leg ulcer*'. It has been further suggested that patients should have a repeat ultrasound within three monthly intervals (Simon et al. 1994). Given these recommendations, 90 days post diagnosis is a generous amount of time in which to expect a Doppler ultrasound assessment is completed.

If the patient's database record had (i) a Read code indicative of Doppler ultrasound or (ii) a record of ankle and/or brachial pressure index measurement, this was deemed indicative of a patient having had an ABPI measurement using Doppler ultrasound. The codes used to identify

records indicative of measurement of ABPI using Doppler ultrasound can be supplied upon request.

First, descriptive analyses were undertaken to explore the frequencies and proportions of incident patients with a database record of an ABPI measurement. For ease of comparison the results of these descriptive analyses are presented separately for each of the three forms of leg ulceration investigated. Next temporal changes in recorded use of ABPI were examined. For each database diagnosis of leg ulceration examined, the frequency and proportion of patients receiving ABPI during each year of the study period was investigated to explore potential temporal trends. A further descriptive analysis of the proportion of leg ulcer patients receiving a database record of ABPI within each practice was performed.

Finally, given that patients are clustered within practices, multilevel logistic models were created to explore the relationship between patient and practice-level variables and the outcome variable. In these analyses the outcome variable was binary; i.e. whether or not the patient had an ABPI measurement in the thirty days prior to or in the ninety days post incident diagnosis of leg ulceration.

One of the key practice level variables, the IMD of the practice, is calculated differently in each UK country. IMD measures used by the different countries (i.e. England, Wales, Scotland, Northern Ireland) contain different domains (e.g. health, crime income and employment) which are weighted differently and are calculated at different geographical units. For example, in England the IMD is measured at the Lower Layer Super Output Area and contains the domain health which is weighted as 13.5. In contrast the IMD in Northern Ireland the IMD is measured at the Super Output Area and has health domain weighted as 15. Therefore the scores produced in different countries are not directly comparable. Pragmatically, it was decided to restrict the multilevel model to analysis of patients visiting practices in England as this was the location of the majority of practices contributing to the GPRD.

4.4.3 Methods for the exploration of initial therapy provision

As was summarised in the literature review, the majority of research and guidance for the treatment of leg ulcers is focused on venous leg ulcers. All three U.K. guidelines for the treatment of venous leg ulcers concluded that the first line therapy that should be offered to patients with venous leg ulcers is compression bandaging (CREST 1998; SIGN 1998; RCN 2006). For arterial and mixed venous-arterial leg ulcers no gold standards of treatment exist (Nelson &Bradley 2007). However, certain treatments such as high compression bandaging are noted as being potentially harmful in patients with underlying arterial disease (RCN 2006).

It has been suggested that complete diagnostic assessment of underlying leg circulation may take up to ninety days to conduct (Margolis et al. 2002). It was therefore clinically reasonable to expect that patients would have received some form of treatment for their leg ulcer within these first ninety days. As with the diagnostic assessment, it was also possible that patients were prescribed a therapy prior to the database diagnosis being recorded. Therefore, therapies prescribed to leg ulcer patients within the first 30 days prior to diagnosis and ninety days post diagnosis were evaluated.

Leg ulcer therapies were defined as those that were (i) listed in Appendix 8, Wound management products and elastic hosiery, of the British National Formulary (Joint Formulary Committee 2008), or (ii) they are one of the following therapies which have been described in the literature as a treatment for leg ulceration, and are routinely prescribed in UK general practice: manuka honey, larval therapy, pentoxyfylline, magnetic leg ulcer wraps, debridement and vacuum assisted wound closure (Eccles &Hollinworth 2005; Jull et al. 2008; Nelson &Jones 2008; NHS Purchasing and Supply Agency 2008; Dumville et al. 2009; Jull et al. 2010). As compression bandages can be prescribed or applied using either a compression bandage kit or by using a combination of bandages an inclusive approach was taken when deciding whether compression bandages were used. Therefore if either a compression bandage or a bandage which can be made into compression bandages were used this was defined as compression bandaging. The definitions of compression bandages used by Dumville et. al. (2009) were replicated. This definition classed crepe bandages, cohesive bandages or Class 3A or 3C bandages as compression bandages.

Database reports of prescriptions for wound care products are coded in the GPRD using a variety of methods. These methods include gprd medcodes, BNF chapter headings and subchapter headings and records made using the brand or generic product names, referred to in the database as Multilex product codes. Rarely, prescriptions were also recorded using Read codes, indicating that an application of the product was made, e.g. compression bandaging. Using these data, leg ulcer therapies were grouped into five categories; compression bandages, other bandages, dressings, stockings or other with the other category including pentoxyfylline, honey, larvae, magnetic therapies, other debridement and vacuum assisted wound closure. The BNF chapter headings used to compile these groupings are shown below in table 4.1. The exact list of gprd medcodes and Multilex product codes used to identify wound therapies in the GPRD can be supplied upon request.

Table 4.1 BNF chapter headings used to classify wound therapies

	Compression bandages*	Other bandages	Dressings	Stockings	Other
BNF chapter heading	Appendix 8 8.2.5 High compression bandages 8.2.6 Extra high performance compression bandages 8.2.10 Multi-layer compression bandaging 8.2.8 Cohesive bandages and other sub sections to identify crepe bandages and class 3A/3C bandages.	Appendix 8 8.2.1 Non extensible bandages 8.2.2 Light weight conforming bandages 8.2.3 Tubular bandages 8.2.4 Support bandages 8.2.7 Adhesive bandages 8.2.9 Medicated bandages	All dressing listed in Appendix 8, 8.1 Wound dressings with the exception of 8.1.9 Surgical absorbents	Appendix 8 8.3.1 Graduated compression hosiery	Chapter 2, 2.6.4 Peripheral vasodilators and related drugs Pentoxyfylline Chapter 13, 13.11.7 Preparations for promotion of wound healing Includes desloughing agents such as sterile larvae and aserbine as well as topical preparations of growth factor.

First, a descriptive analysis of the frequency and proportion of all database records of wound care therapies prescribed to incident leg ulcer patients was undertaken, with results presented separately for each database diagnosis of leg ulceration. Second, the relationship between database records of therapy provision and practice level deprivation was evaluated in the subset of patients with a database record of incident venous leg ulceration. In keeping with earlier analyses, these results were restricted to exploration of patients attending English practices. Third, a descriptive analysis was undertaken to examine the proportion of venous leg ulcer patients within each practice who had a database record of receiving compression bandages. Fourth, analyses were performed to examine if any patient or practice level variables were statistically associated with receiving a prescription for compression therapy. As patients are nested within practices, multilevel logistic models were used to examine the relationship between these characteristics and the odds of receiving a database record of prescription for compression therapy. For consistency with the earlier results of diagnosis, these analyses were restricted to exploration of the incident cohort of venous leg ulcer patients attending practices located in England.

4.4.4 Methods for the exploration of referrals

Referral decisions made by primary care providers for leg ulcer care have not been comprehensively explored in the UK. There is no consistent referral guidance provided by the three UK guidelines for the care of leg ulcers. Indeed all three were found to provide different temporal and prognostic recommendations (CREST 1998; SIGN 1998; RCN 2006). No studies were located that examined patient outcomes following referral from general practice to other health care practitioners or services. Both the CREST (1998) and the RCN (2006) guidelines recommend that patients who have shown no improvement following 12 weeks of treatment should be referred. However, the SIGN guidelines (1998) recommend referring patients by 12 weeks if the ulcer had not improved with the use of compression therapy and CREST guidance (1998) within 12 months if the ulcer failed to heal. Given these differing recommendations, an inclusive approach was employed when investigating referrals from general practice and it was therefore decided to examine referrals made any time in the year following diagnosis.

Referrals were examined in three stages. First, the entire range of health and social care professionals that leg ulcer patients were had a database record of being referred to over the entire study period is described. Frequencies and proportions of the full range of health professional groups that patients had a database record of being referred to are reported. These results are presented separately for each of the three database diagnoses of leg ulcer examined. Second, database records of referrals made to the specific range of health professionals providing specialist treatment for persons with leg ulcers were examined. The health professional groups deemed in this analysis as providing specialist leg ulcer care were; tissue viability nurses, podiatrists, chiropodists and vascular surgeons. Frequencies and proportions of patients with a database record of being referred to these clinical practitioners were calculated. Separate descriptive analyses were performed for patients with each of the three database diagnoses of leg ulceration examined. The code list used to identify records of referrals in the GPRD database can be supplied upon request. Third, multilevel logistic models were developed to examine the effect of explanatory variables on the odds of receiving a database record of a referral. The first of these models examined the relationship between patient and practice level variables and having a database record of receiving any type of specialist leg ulcer referral in year following diagnosis. The final multilevel model was undertaken to examine the relationship between patient and practice level variables and having a database record of receiving a referral of any kind.

Results of all statistical tests were assumed to be statistically significant when the p values were less than or equal to 0.05. Confidence intervals of point estimates were also reported.

The results of multilevel logistic models are unreliable if there are fewer than five participants in any group (Moineddin et al. 2007; Theall et al. 2008). In this study, this equates to there being fewer than five patients with a particular diagnosis of leg ulceration in any practice. If this was the case in any of the proposed analyses, multilevel logistic regression models were not produced.

Model selection was determined by calculation of the Akaike's Information Criterion (AIC). The AIC value is the sum of the deviance and two times the number of parameters included in the model (Sellström et al. 2003). The model with the smallest AIC value represents the model that best fits the data.

4.5 Results

4.5.1 Summary characteristics of the prevalent cohort

The GPRD records were searched to identify all patients with a prevalent database record of a venous, arterial or mixed venous arterial leg ulceration occurring during the study period of January 2001 to December 2006. The patient characteristics of the prevalent cohort with a database diagnoses of venous, arterial and mixed venous arterial leg ulcers in the GPRD are shown below in table 4.2.

Table 4.2 Patient characteristics of the prevalent cohort stratified by database diagnosis of leg ulcer

	Venous ulcers	Arterial ulcers	Mixed venous-arterial ulcers
Total n (%)	20682 (97.2)	417 (2.0)	162 (0.8)
Female n (%)	12889 (62.3)	227 (54.4)	106 (65.4)
Mean age (SD) Median, range (years)	73.96 (14.35) 77, 18-109	77.58 (12.04) 80, 21-104	78.96 (12.39) 82, 40-104

The majority of prevalent leg ulcer patients had a database diagnosis of venous leg ulceration, comprising over 97.2% of all documented leg ulcer patients in the GPRD throughout the study period. The next largest patient group were those with a database diagnosis of arterial and lastly those with a database diagnosis of prevalent mixed venous arterial leg ulcers. For all three database diagnoses of leg ulceration examined the majority of prevalent patients were female. The gender division was less evident for patients with a prevalent database diagnosis of arterial ulcers, where only slightly more females than males had a database record of the condition (54% *vs.* 46%).

4.5.2 Results of age and gender related trends in average period prevalence

The period prevalence of venous leg ulceration was first examined. The results presented in Figure 4.2 below show the results of average period prevalence rates of venous leg ulceration stratified by gender and ten year age category.

Figure 4.2 Average period prevalence of venous leg ulceration stratified by age group and gender

Average period prevalence rates of venous leg ulceration were shown to rise with age, most steeply from age 68 onwards reaching a high of over 861 per 100,000 persons for males and over 1200 per 100,000 person for females. From age 58 onwards, average prevalence rates of venous leg ulceration were found to be higher for females than males.

Next, an exploration of the average period prevalence rates of arterial leg ulceration stratified by age category and gender was conducted. These analyses can be seen below in figure 4.3.

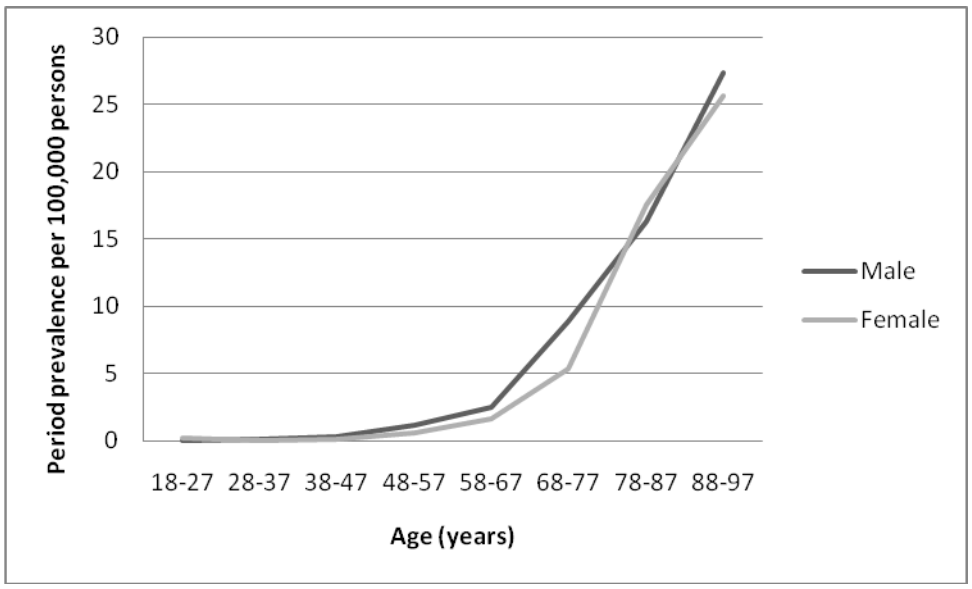

Figure 4.3 Average period prevalence of arterial leg ulceration stratified by age group and gender

Rates for both genders were very low up until the age of 67 years, with observed rates below 5 per 100,000 persons. From 68 years onwards, rates rose steeply in both genders reaching a high of greater than 25 per 100,000 persons in both genders from the age of 88 years onwards. Rates of arterial leg ulceration were shown to be considerably lower than those observed for venous leg ulceration.

Finally, the relationship of age group and gender with the average period prevalence rates of mixed venous arterial leg ulceration was examined and shown below in figure 4.4.

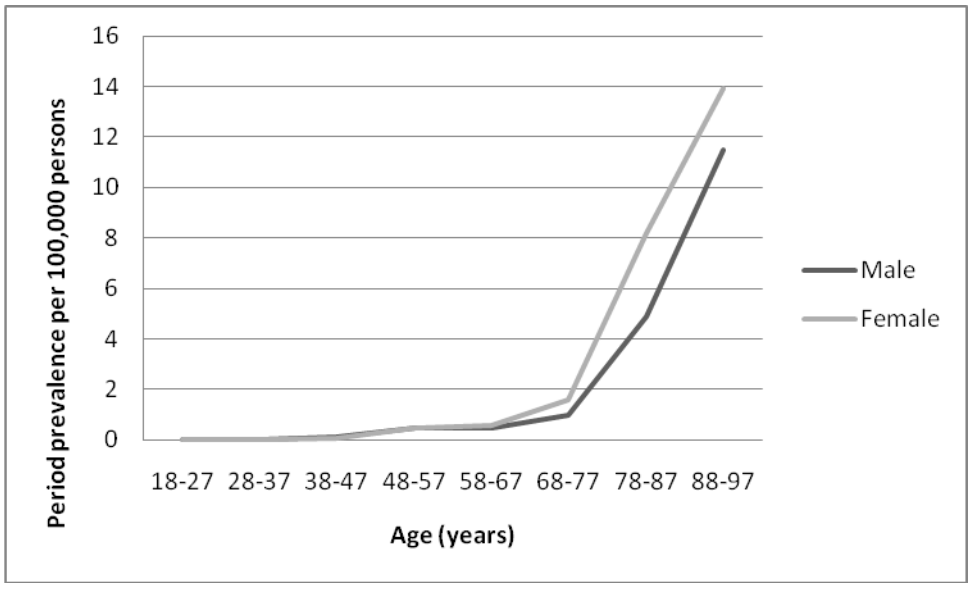

Figure 4.4 Average period prevalence of mixed venous arterial leg ulceration stratified by age group and gender

Average prevalence rates of mixed venous arterial leg ulceration were lower than for the other two diagnoses of leg ulceration examined. Rates only increased above four per 100,000 peoples as age exceeded 78 years. In common with the earlier results of venous prevalence, rates of mixed venous arterial prevalence in females were higher than those observed for males in every age category examined.

4.5.3 Results of the examination of prevalence rates using negative binomial and/or Poisson regression

The descriptive analyses performed thus far have been restricted to the exploration of the stratified effects of age categories and gender on prevalence rates of leg ulcers. To produce more comprehensive findings multivariable regression analyses were used to examine the multiple effects of age, gender and study year on prevalence rates. Using Poisson or negative binomial regression methods as were appropriate to the data separate models were created to explore the effect of these explanatory variables on all three database diagnoses of leg ulceration examined.

First, negative binomial regression analysis was used to examine the effects of explanatory variables on prevalence rates of venous leg ulcers. The results of this analysis can be seen below in Table 4.3. These results showed that age, gender and year of the study all independently contributed to the observed variations in prevalent rate ratios of venous leg ulceration. Patients' age had the largest positive statistically significant effect with rates increasing by 8.1% (95% C.I. 8.0-8.2) for each year of increasing age. Female gender was associated with a 7% increase in the risk of prevalence of venous leg ulcers compared to males, whilst rates were also shown to be increasing by approximately 2% (95% C.I. 0.5-2.9) per year over the study period.

Table 4.3 Effect of gender, year and age on prevalence rate ratios of venous leg ulcers

Explanatory variable	PRR (95% CI)	p-value
Gender		
Male	1	
Female	1.071 (1.028, 1.117)	<0.001
Year	1.017 (1.005, 1.029)	<0.001
Age (year)	1.081 (1.080, 1.082)	<0.001

$\chi 2$ 3, 1139=2983.90, P<0.001, pseudo R2=0.353, α for dispersion 0.033 (95% CI 0.026-0.042)
PRR prevalence rate ratio CI confidence interval

Next the relationship between explanatory variables and the prevalent rate ratios of arterial leg ulceration was examined using negative binomial regression. Results of the regression analyses and the resulting prevalence rate ratios are shown below in table 4.4. Of the variables examined, only age was shown to have a statistically significant relationship with prevalence rates ratios of arterial leg ulceration. With each year of increasing age there was an 11.5% increase (95% C.I.

10.4-12.6) in the risk of having prevalent arterial leg ulcers. Neither gender nor study year were shown to have a statistically significant relationship with prevalence rate ratios of arterial leg ulceration.

Table 4.4 Effect of gender, year and age on prevalence rate ratios of arterial leg ulcers

Explanatory variable	PRR (95% CI)	p-value
Gender		
Male	1	
Female	1.393 (0.980, 1.980)	0.064
Year	0.962 (0.862, 1.073)	0.487
Age	1.115 (1.104, 1.126)	<0.001

χ2 3, 314=411.74, P<0.001, pseudo R2=0.41, α for dispersion 1.478 (95% CI 1.249-1.749)
PRR prevalence rate ratio CI confidence interval

Finally, the relationship of explanatory variables with prevalent rate ratios of mixed arterial leg ulceration was examined. The results of this analysis are shown below in Table 4.5.

Table 4.5 Effect of gender, year and age on prevalent rate ratios of mixed venous-arterial leg ulcers

Explanatory variable	PRR (95% CI)	p-value
Gender		
Male	1	
Female	1.181 (0.850, 1.641)	0.321
Year	1.452 (1.354, 1.557)	<0.001
Age (year)	1.108 (1.095, 1.121)	<0.001

χ2 3,650=684.26, P<0.001, pseudo R2=0.471, Goodness of fit test 487.24 P=1.00
PRR prevalence rate ratio CI confidence interval

Only two of the three explanatory variables included in the model were shown to have a statistically significant relationship with prevalent rate ratios of mixed venous arterial leg ulceration. With each increasing year of age there was a 10.8% increase (95% C.I. 9.5-12.1) in prevalence rate ratios of mixed venous arterial leg ulcers. Whilst increasing year of study was shown to be associated with a 45% increase (95% C.I. 35.4-55.7) in the prevalent rate ratios of mixed venous arterial leg ulceration.

4.5.4 Summary characteristics of the incident cohort

The baseline characteristics of the incident leg ulcer cohort identified in the GPRD are shown below in Table 4.6. The presented results are stratified by database diagnosis of leg ulceration.

Table 4.6 Patient characteristics of the incident cohort stratified by database diagnosis of leg ulcer

	Venous ulcers	Arterial ulcers	Mixed venous-arterial ulcers
Total, N (%)	16,920 (97.6)	301 (1.7)	110 (0.7)
Female, N (%)	10,674 (63.1)	166 (55.15)	76 (69.09)
Mean age (SD) Median, range	73.62 (14.39) 77 (18-109)	76.67 (12.39) 79, 21-98	80.22 (12.49) 83 (40-104)

Over 17,000 patients had a database diagnosis of incident leg ulceration occurring during the study period of 2000 to 2006. Most of the incident cohort had a database diagnosis of venous leg ulcers, (97.6%); smaller numbers of leg ulcer patients had a database diagnosis of arterial leg ulcers (1.7%) or mixed venous-arterial leg ulcers (0.6%).

Gender differences were evident for every database diagnosis of leg ulcers examined with females forming over half of the cohort. These were most pronounced amongst patients with venous and mixed venous arterial leg ulceration, where females comprised over 63% of all patients. The mean age of patients at their incident consultation was in excess of 73 years, ranging from 18 to 109 years, varying by the recorded database aetiological classification of incident leg ulceration.

4.5.5 Results of the effect of age and gender on incidence density rates

First, descriptive analyses were undertaken to examine the relationship between age, gender and incidence rates over the entire study period. The results are stratified by 10 year age category, from ages 18 to 98 years and by gender. Graphs of these results are first presented for venous, followed by arterial and finally mixed venous arterial database diagnoses of leg ulceration.

Figure 4.5 Average annual incidence density of venous leg ulceration per 100,000 person years, stratified by age category and gender

Shown above in Figure 4.5 are the average annual incidence density rates of venous leg ulcers, stratified by age and gender. Average incidence density rates of venous leg ulceration were shown to rise with age for both genders, with rates for females observed to be higher than those for males across all age categories.

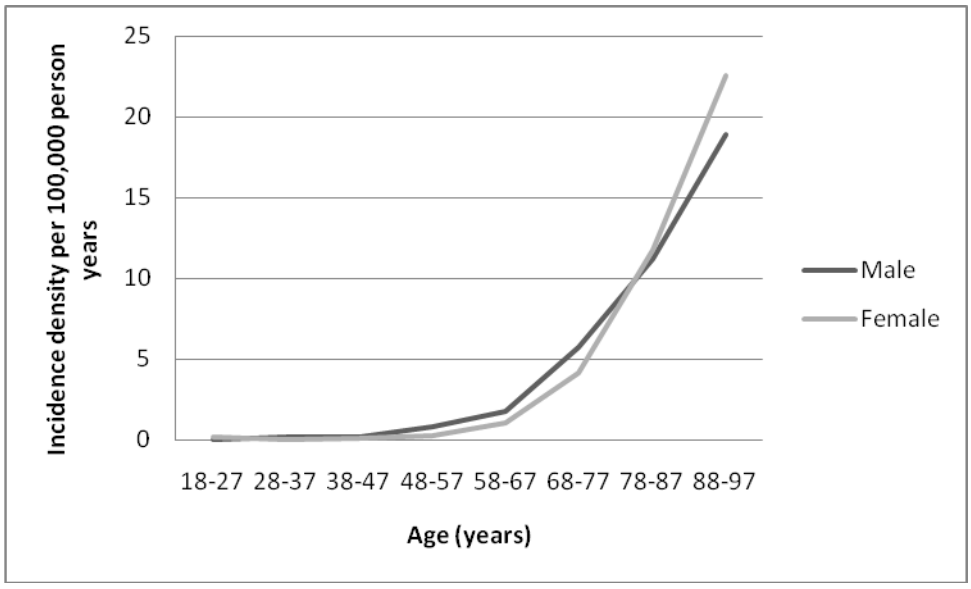

Figure 4.6 Average incidence density of arterial leg ulceration per 100,000 person years, stratified by age and gender.

Next, average annual incidence density rates of arterial leg ulceration were calculated. These results were stratified by age category and gender, and can be seen above in figure 4.6. Rates for both genders increased with age, although there did not appear to a consistent relationship of rates with gender. Rates of incident arterial leg ulceration were shown to be consistently lower than those observed for venous leg ulceration.

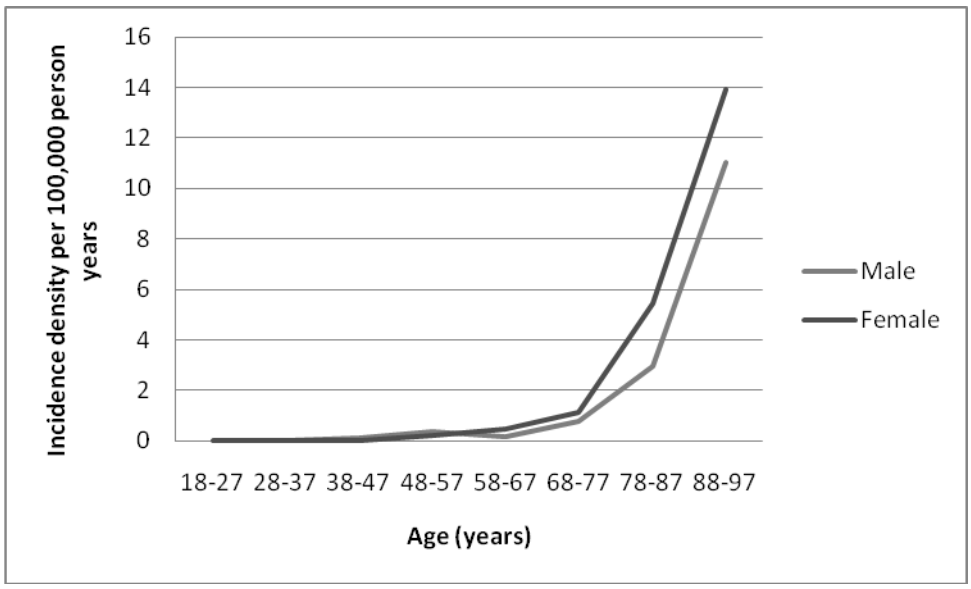

Figure 4.7 Average incidence density of mixed venous arterial leg ulceration per 100,000 person years, stratified by age and gender

Finally, average annual incidence density rates of mixed venous arterial leg ulceration stratified by age and gender were calculated and are shown in Figure 4.7. Consistent with the other two forms of leg ulceration examined, incidence density rates were shown to increase with age for both males and females. Rates for females were higher than those observed for males across all age categories examined which was also consistent with the results of incident venous leg ulceration. The incidence density rates of mixed venous arterial leg ulceration were found to be lower than those observed for both venous and arterial leg ulcers.

4.5.6 Results of the examination of incidence density rates using negative binomial regression and/or Poisson regression

Descriptive analyses have provided an introduction to the relationships between age and gender of the incidence density rates of venous, arterial and mixed venous arterial leg ulceration. Further analyses using regression were undertaken quantifying the multiple effects of gender, age and study years on incidence rate ratios. The regression methods used were either Poisson or negative binomial regression methods as were appropriate to the data. The effect of covariates on incidence rate ratios of venous leg ulceration was examined followed by arterial and then mixed venous arterial leg ulceration.

Shown below in table 4.7 are the results of the adjusted analyses of the association of covariates with incidence rate ratios of venous leg ulcers using negative binomial regression.

Table 4.7 Effect of gender, year and age with incidence rate ratios of venous leg ulcers

Explanatory variable	IRR (95% CI)	p-value
Gender		
Male	1	
Female	1.151 (1.105, 1.198)	<0.001
Year	0.976 (0.966, 0.985)	<0.001
Age (year)	1.081 (1.1080, 1.083)	<0.001

χ2 3, 1320=3308.87, P<0.001, pseudo R2=0.353, α for dispersion 0.029 (95% confidence interval 0.022-0.038)
IRR Incidence rate ratio CI confidence interval

For venous leg ulcer patients, the explanatory variables found to a have a statistically significant relationship with the incidence density rate ratios of venous leg ulceration were the same as those observed earlier for venous period prevalence rate ratios. Once again age, gender and study year were all found to have statistically significant relationships with incident rate ratios of venous leg ulcers. Adjusted analysis showed with each year of increasing age 8% increase in risk of developing venous leg ulcers (95% C.I. 8.0-8.3). Females were shown to have a 15% greater risk of developing venous leg ulceration compared to males (95% C.I. 10.5-19.8). Finally, rate ratios showed that each increasing year of the study was associated with a 3.4% decrease in risk of developing venous leg ulcers.

Next, the effects of explanatory variables on incidence density rate ratios of arterial leg ulcers were examined using Poisson regression. These results are shown below in table 4.8.

Table 4.8 Effect of gender, year and age on the incidence rate ratios of arterial leg ulcers

Explanatory variable	IRR (95% CI)	p-value
Gender		
Male	1	
Female	0.795 (0.631, 1.002)	0.052
Year	0.940 (0.888, 0.996)	0.034
Age (year)	1.101 (1.092, 1.111)	<0.001

χ2 3, 1320=740.16, P<0.001, pseudo R2=0.39, Goodness of fit test χ2 654.79 P=1.00
IRR Incidence rate ratio CI confidence interval

Incidence rate ratios of arterial leg ulceration shared a statistically significant relationship with patient's age and study year. Rates increased by 10.1% (95% C.I. 9.2-11.1) for each year older that patients were and decreased by 6% per year (95% C.I. -12 to -0.1) over the study period. Gender had no statistically significant relationship with the development of incident arterial leg ulcers.

The relationship between explanatory variables and incidence rates of mixed venous arterial leg ulcers was examined using Poisson regression. The results of this analysis are shown below in Table 4.9.

Table 4.9 Effect of gender, year and age on incidence rate ratios of mixed venous arterial leg ulceration

Explanatory variable	PRR (95% CI)	p-value
Gender Male Female	 1 1.338 (0.887, 2.017)	 0.164
Year	1.115 (1.012, 1.139)	0.028
Age (year)	1.121 (1.104, 1.139)	<0.001

χ2 3, 1320=356.63, P<0.001, pseudo R2=0.37, Goodness of fit test χ2 413.13 P=1.00
IRR Incidence rate ratio CI confidence interval

Study year and patient age were both shown to have a positive statistically significant relationship with incidence rate ratios of mixed venous arterial leg ulcers, however no relationship was observed with gender. With each increasing year of age patients had a 12% increase in risk (95% C.I. 10.4-13.9), and with each increasing year of the study rates were shown to increase by 11.5% per year (95% C.I. 1.2-13.9).

4.5.7 Results of the exploration of the initial ulcer assessment

Between 2000 to 2006, 16,920 patients met the criteria of having a database diagnosis of incident venous leg ulceration. Of these patients, 10.6% (n=1799) had a database record of receiving an ABPI assessment within the 30 days prior to or in the 90 days post incident diagnosis. Over the same time period, 466 patients were found with a database diagnosis of incident arterial leg ulcers and of these patients, 12% had a record of receiving an ABPI assessment. Patients with a database diagnosis of incident mixed leg ulcer (n=110) were the most likely to have a database record of receiving an ABPI assessment at 21.8%. The proportion of patients with a database record of receiving ABPI assessment during each year of the study period is shown below in table 4.10. These results are stratified by database diagnosis of leg ulceration. The results show that there has been an increase in the documented proportion of all leg ulcer patients receiving an ABPI assessment throughout the study period.

Table 4.10 Frequency and proportion of patients receiving an initial assessment of ABPI, stratified by study year and database leg ulcer diagnosis

	Venous leg ulcer n (%)	Arterial leg ulcer n (%)	Mixed venous arterial leg ulcer n (%)
2000	130 (6.2)	4 (8.9)	5 (55.6)
2001	208 (8.8)	1 (2.2)	1 (14.3)
2002	229 (9.2)	2 (4.8)	3 (20.0)
2003	266 (10.2)	5 (12.5)	2 (8.7)
2004	284 (11.1)	10 (19.6)	4 (17.4)
2005	358 (14,5)	6 (14.0)	3 (20.0)
2006	324 (13.9)	8 (22.8)	6 (31.6)

Next, variation in proportions of venous leg ulcer patients receiving a record of ABPI assessment within each of the 433 practices was investigated. The mean proportion of patients with a record receiving ABPI assessment within practices was 22%, the range varying from zero to 100%.

The cohort of patients with a database diagnosis of incident venous leg ulceration was sufficiently large to perform further analysis using multilevel logistic regression. This enabled the examination of the relationship between variables and the odds of receiving a database record of ABPI assessment to be conducted. As the Index of Multiple deprivation (IMD) of the practice was calculated differently in each country of the UK scores from different countries could not be compared. A pragmatic decision was made to include data from patients attending practices in England only as this is where the majority of leg ulcer patients were located. The results are based on 14,642 incident venous leg ulcer patients attending 366 practices in England, an average of 40 patients per practice. The patients included in this analysis constitute 86.5% of all incident venous leg ulcer patients identified in the GPRD. This same sub-cohort was used for all multilevel analyses performed in this chapter.

The results of these analyses are shown below in table 4.11.

Table 4.11 Results of multilevel logistic regression analyses of diagnostic assessment

	Model with patient level variables only	**Model with patient and practice level variables**	**Model with patient and practice level variables**
	Model 1	**Model 2**	**Model 3**
Individual level variables	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age (year)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.98 (0.97-0.99)
Gender Male Female	 1 0.86 (0.74-0.99)	 1 0.86 (0.74-1.01)	 1 0.86 (0.74-0.99)
Year of diagnosis	1.21 (1.15, 1.28)	1.21 (1.15, 1.28)	1.21 (1.15, 1.28)
Practice level variable			
Deprivation score		0.98 (0.97-0.99)	
Deprivation ranke 0 (low deprivation) 1 2 3 4 (high deprivation)			 1 0.33 (0.29-1.16) 1.13 (0.64-2.01) 0.61 (0.34-1.12) 0.41 (0.22-0.75)
Intercept (SE)	-384.61 (54.30)	-382.65 (58.13)	-383.86 (54.67)
Intra-class correlation co-efficient (%)	78.35	51.3	50.9
Akaike's information criterion	9370.72	9363.71	9363.20

In Model one the analysis examined the relationship of patient level variables and the odds of having a database record of receiving an ABPI assessment. All included variables were found to have a statistically significant relationship with the odds of receiving ABPI assessment. Each year post 2000 that patients were diagnosed with venous leg ulceration was associated with a 21% increase in the odds of receiving an ABPI assessment (95% C.I.1.15-1.28). Both age and gender related inequalities were shown to exist despite this increase in ABPI usage over the study period. Each increasing year of patient age was associated with a two per cent reduction in the odds of ABPI assessment (95% C.I. 0.97-0.99) and females were 14% (95% C.I. 0.74-0.99) less likely than males to have a database record of receiving an ABPI assessment.

In the analysis conducted to create model two, both patient and practice level variables were simultaneously examined. The practice level variable that was included in the model was the IMD score of the practice. Higher scores indicated that the practice was located in a more deprived area. The inclusion of this practice level variable adjusted the direction and magnitude of some but not all of the other patient level variables included in the model. The effect of patient age and study year remained, however there was no longer a statistically significant relationship between gender and the odds of receiving ABPI assessment. A higher IMD score (i.e. higher deprivation)

was associated with a 2% decrease in odds (95% C.I. 0.97-0.99) of having a record of receiving ABPI assessment.

To further interpret the result of the relationship between practice level deprivation and the odds of ABPI assessment model three was created. This model contained the same variables as model two, however IMD was examined as a fifth rank. As can been seen above in table 4.11, the point estimates of other variables included in the model did not change ,with the exception of gender which reverted back to the same statistically significant value as model one. Female gender was associated with a 14% decrease in the odds of receiving ABPI assessment (95% C.I. 0.74-0.99). When the results were presented for fifths of the IMD score of the practices, reductions in the odds of having a database record of receiving ABPI assessment were only evident for patients attending practices in the most deprived fifths. These patients were shown to be nearly 60% less likely to have a database record of receiving ABPI assessment compared to their peers attending practices in the least deprived fifths, OR 0.41 (95% C.I. 0.22-0.79).

Model fit statistics were calculated and Akiake's information criteria values showed that the model with the best fit to the data was model three, the final model created. Despite the reported use increasing over time the results of this analysis showed that there were deprivation, age and gender inequalities in the reported provision of ABPI assessment.

4.5.8 Results of the exploration of initial therapy provision

Records of patients' with incident venous leg ulcers were searched for reports of therapies, prescribed or provided in surgery, reported as being provided in the thirty days prior to or in the ninety days post incident diagnosis. The full details of all reported therapies prescribed or applied in general practice throughout the study is shown in appendix D. These results are stratified by database diagnosis of leg ulceration.

First, these results showed that not all leg ulcer patients had a database record of having received a leg ulcer therapy or prescription during the study period. The majority of venous leg ulcer patients (73.5%) had a record of being given provided with or allocated a prescription for a leg ulcer therapy, whereas only 67.1% of arterial leg ulcer patients had a record of a prescription or provision of a leg ulcer therapy. Patients diagnosed with mixed venous arterial ulcers were most likely to have a documented treatment, with 97.2% having a record of receiving a prescription or leg ulcer treatment. The most commonly prescribed or provided therapies for leg ulcer patients of all aetiologies were non compression bandages and dressings.

Next, the records of therapies prescribed and provided to patients with venous leg ulcers were further interrogated to investigate the relationship between the type of therapy prescribed and the deprivation fifth rank of the treating practice. In keeping with earlier analysis, exploration of practice level deprivation was restricted to the examination of therapies prescribed patients attending practices in England. These results are shown below in table 4.12. The only therapeutic group that showed any relationship with practice level deprivation was the 'other therapy' group. The 'other therapy' group consisted of prescriptions for larval therapy, honey, debridement and pentoxyfylline. For this therapeutic group, higher proportions of patients attending practices in more deprived area were found to have a database record of having received a prescription for these therapies. The results showed no relationship between therapeutic class and practice level deprivation or for those patients without a record of a prescription.

Table 4.12 Relationship between prescriptions issued to venous leg ulcer patients and practice level deprivation rank

Deprivation rank	1 (low deprivation)	2	3	4	5 (high deprivation)	Total
Compression	484 (21.0)	330 (14.3)	542 (23.5)	457 (19.8)	494 (21.4)	2,616
Bandages	1,019 (19.7)	792 (15.3)	1,229 (23.8)	1,035 (20.0)	1,095 (20.2)	5,170
Dressings	1,918 (19.4)	1,648 (16.6)	2,336 (23.6)	2,008 (20.3)	1,999 (20.2)	9,099
Stockings	446 (21.1)	429 (20.3)	476 (22.5)	406 (19.2)	362 (17.1)	2,119
Other therapies	5 (13.9)	6 (16.7)	4 (11.1)	8 (22.2)	13 (36.1)	36
*Any therapy	2,757 (22.0)	2,151 (17.2)	2,741 (21.9)	2,457 (19.5)	2,436 (19.4)	12,542
None	919 (21.0)	728 (16.6)	865 (19.8)	946 (21.6)	920 (21.0)	4,378
Total	3,676 (21.7)	2,879 (17.0)	3,606 (21.3)	3,403 (20.1)	3,356 (19.8)	16,920

* Proportions of prescribed therapies will not add up 100 as patients were prescribed multiple therapies during the time period investigated.

Prescription of compression therapy was the main variable of interest, given the strong evidence base for its usage as a first line therapy for venous leg ulcers (O'Meara et al., 2009). 15.5% (n=2616) of patients with a database diagnosis of venous leg ulcers had a database record indicating that they received a prescription or were treated in practice with compression therapy during the study period. This compares to 8.6% (n=26) of patients with arterial leg ulceration and 28.2% (n=31) of patient's with mixed venous arterial leg ulceration. Shown below in table 4.13 is the proportion of patients with a record receiving a prescription for compression therapy during each year of the study period. These results are stratified by database diagnosis of leg ulceration.

Table 4.13 Proportion of leg ulcer patients prescribed compression therapy, stratified by database diagnosis of leg ulcer

	Venous leg ulcer n (%)	Arterial leg ulcer n (%)	Mixed venous arterial leg ulcer n (%)
2000	362 (17.3)	2 (4.4)	3 (33.3)
2001	365 (14.7)	7 (15.5)	2 (28.6)
2002	374 (15.0)	4 (9.5)	2 (13.3)
2003	371 (14.2)	4 (10.0)	5 (21.7)
2004	400 (15.6)	1 (2.0)	5 (33.3)
2005	411 (16.7)	4 (9.3)	3 (15.8)
2006	333 (14.3)	4 (12.9)	11 (50.0)

The results from table 4.13 above indicated that there were variations in the proportion of patients with a database records of an initial prescription for compression therapy throughout the study period, although no consistent increase or decrease in use was observed.

The final descriptive analysis consisted of examining the proportion of venous leg ulcer patients within each practice who had a record of receiving compression bandaging. The mean proportion of leg ulcer patients within each practice receiving compression was 15%. This value was shown to range from zero to 45% of all venous leg ulcer patients within different practices.

As there were sufficient numbers of patients with venous leg ulceration, examination of potential explanatory variables associated with a database record of prescription or provision of compression therapy was conducted using multilevel logistic regression. In common with the earlier results exploring diagnosis, analyses were restricted to incident venous leg ulcer patients attending English practices. The results of these analyses are shown below in Table 4.14.

Table 4.14 Results of the multilevel analysis of initial therapy provision of compression therapy

	Model with patient variables only	**Model with patient and practice variables**	**Model with patient and practice variables**
	Model 1	**Model 2**	**Model 3**
Individual level variables	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age (year)	1.01 (1.01, 1.03)	1.02 (1.01-1.03)	1.01 (1.01-1.02)
Gender Men Women	 1 0.93 (0.74, 1.15)	 1 0.93 (0.74, 1.15)	 1 0.93 (0.74, 1.15)
Year of diagnosis	0.96 (0.91, 1.02)	0.96 (0.91-1.01)	0.96 (0.92-1.01)
Practice level variable			
Deprivation score		0.99 (0.99-1.01)	
Deprivation rank 1 (low deprivation) 2 3 4 5 (high deprivation)			 1 0.54 (0.27-1.05) 0.82 (0.45-1.52) 0.71 (0.38-1.32) 0.84 (0.46-1.55)
Intercept (SE)	68.52 (51.57)	68.48 (55.93)	68.52 (45.02)
Intra-class correlation Coefficient (%)	29.74	29.74	29.54
Akaike's Information Criterion	12318.35	12320.34	12322.56

The first model that was created, model one, examined the relationship between having a databse record of prescription or provision of compression therapy and patient level variables only. These variables were patient age, gender and year of diagnosis. Patient's age was the only variable found to be statistically associated with the odds of having a record of receiving compression therapy. With each year of increasing age patients had a one per cent increase in the odds (95% C.I. 1.01-1.03) of having a database record of receiving a prescription or application of compression therapy.

Model two included the same patient level variables as model one as well as an additional practice level variable. The extra practice level variable added to this model was the IMD score of the practice that the patient attended. The inclusion of practice level IMD only slightly modified the confidence intervals around the estimate for year of diagnosis and did not change the direction or

magnitude of the effect of any of the patient level variables from the results observed for model two. Practice level IMD score was not shown to have a statistically significant relationship with the odds of receiving a prescription for compression therapy, OR 1.0 (95% C.I 0.99-1.01).

Model three was created using the same patient and practice level variables as model two, however in this analysis IMD of the practice was examined as a fifth. This model was created to allow further interpretation of the effect of practice level IMD on the odds of receiving compression therapy. All other co-variates included in the model produced identical results to model two. Deprivation fifths did not show any statistically significant association with the odds of receiving a prescription for compression therapy.

Model selection using Akaike's information criteria showed that model one, the model with patient level covariates only, was the best fit to the data. These results demonstrate that each increasing year of patient age had a small increase in the odds of being prescribed compression therapy for the treatment of their incident venous leg ulcers. These results demonstrate that there were no gender, deprivation or temporal inequalities evident although there are age related inequalities in the prescription of compression therapy.

4.5.9 Results of exploration of referrals

Referrals were examined in four stages. First, the frequency and proportion of referrals made to any health care provider in the year following incident diagnosis were examined. Patients diagnosed with arterial and mixed venous arterial leg ulceration were most likely to be referred in the year following diagnosis with 59.4% and 44.5% referred respectively. In comparison, only 36.2% of venous leg ulcer patients had a record of receiving a referral in the year post diagnosis.

Second, the frequency and proportion of referrals deemed to be leg ulcer related made within a year of diagnosis were examined. Providers deemed to be leg ulcer specific were tissue viability nurses, podiatrists, chiropodists and vascular surgeons. The full details of these two descriptive analyses are presented in appendix E. Leg ulcer specific referrals were shown to follow similar trends, with patients whose ulcers were diagnosed as arterial and mixed venous arterial being more likely to have a record receiving referrals compared to patients with venous leg ulcers. Rates of leg ulcer specific referrals comprised less than half of all referrals made, with 24.5% and 16.4% of referrals for patients whose ulcers were diagnosed as arterial and mixed venous leg ulcer and 15% of all referrals reported were for patients with venous leg ulcers. The most common leg ulcer specialist group that patients with all three diagnoses of leg ulceration were referred to was Dermatology. The proportion of venous leg ulcer patients within each practice receiving a leg ulcer related referral was also examined. The mean proportion of patients within each practice

that were referred was 10.4%. This figure ranged from zero to 71% of all venous leg ulcer patients who had a leg ulcer specific referral within each practice.

Third, in the subgroup of patients with a database diagnosis of incident venous leg ulceration further exploration of the explanatory variables hypothesised to influence leg ulcer specific referral was undertaken using logistic regression. Although it had originally been intended to use multilevel logistic regression the data failed to converge in a multilevel logistic model. The decision was therefore made to explore these data using a standard logistic regression model. As this model was restricted to a single level of analysis, only patient level variables were included. In keeping with the methods used to examine diagnosis and therapy these results were also restricted to the analysis of patients attending practices in England. The results of this analysis can be seen below in table 4.15.

Table 4.15 Exploration of specialist leg ulcer referral in venous leg ulcer patients using logistic regression

Individual level variables	OR (95% CI)
Age (year)	0.99 (0.99-0.99)
Gender Male Female	 1 0.92 (0.81-1.04)
Year of incident diagnosis	1.14 (1.11-1.17)

Adjusted logistic regression analysis was used to examine the relationship of patient age, gender and year of diagnosis with database records of specialist leg ulcer referrals. Of the included variables, year of diagnosis and patients' age were statistically associated with the odds of being referred for specialist leg ulcer care. Each increasing year of diagnosis was associated with a 29% increase in the odds of referral to a specialist leg ulcer care provider (95% C.I. 1.27-1.30). With each increasing year of age patients were found to have a small but significant decrease in the odds of receiving a specialist leg ulcer referral OR 0.99 (95% C.I. 0.99-0.99).

Fourth, all database records of referrals provided to leg ulcer patients, irrespective of the care provider, were examined and the effect of patient and practice level variables evaluated using multilevel logistic regression. In keeping with all earlier analysis these results were restricted to the cohort of patients with a database diagnosis of venous leg ulceration who had attended practices in England. These results are shown below in table 4.16.

Table 4.16 Exploration of all referrals provided to venous leg ulcer patients using multilevel logistic regression

	Model with patient variables only	**Model with patient and practice variables**	**Model with patient and practice variables**
	Model 1	**Model 2**	**Model 3**
Individual level variables	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age median centred	1.01 (1.00-1.02)	1.01 (1.00-1.02)	1.01 (1.00-1.02)
Gender Men Women	 1 0.89 (0.79-1.01)	 1 0.89 (0.79-1.01)	 1 0.89 (0.79-1.01)
Year of diagnosis	1.27 (1.17-1.37)	1.27 (1.18-1.36)	1.27 (1.19-1.35)
Practice level variable			
Deprivation score		0.99 (0.98-1.01)	
Deprivation rank 1 (low deprivation) 2 3 4 5 (high deprivation)			 1 0.86 (0.51-1.46) 1.03 (0.63-1.68) 1.87 (1.12-3.12) 1.40 (0.86-2.82)
Intercept (SE)	-475.60 (78.8)	-475.92 (73.10)	-475.74 (66.6)
Intra-class correlation Coefficient (%)	16.1	56.1	63.0
Akaike's Information Criterion	17464.6	17192.5	17190.5

The analysis conducted to create the first model included only patient level variables; these being age, gender and study year. Of these variables only age and study year were found to be associated with having a database record of a referral in the year proceeding incident diagnosis of venous leg ulceration. Each increasing year of age was associated with a one per cent increase in the odds of having a database record of receiving a referral (95% C.I. 1.00-1.02). As the study year increased, the odds of having a database record of receiving any referral increased by 27% (95% C.I. 1.17-1.37).

The analysis conducted to create the second model included both patient and practice level variables. The patient level variables included were the same as those included in the first model and no changes were observed in either the direction of magnitude of effects of these variables. The inclusion of the practice level variable, the IMD score of the practice, did not produce a

statistically significant result. This indicated that there was no association between practice level deprivation and odds of having a database record of referral.

In the third model created the same patient and practice level variables were included as for model two, only this time practice level deprivation was examined as a fifth. The inclusion of practice level deprivation fifth did not change the direction or magnitude of the estimates of the patient level variables included in the models from the estimates produced in model two. The results of model selection using Akiake's information criterion showed that this final model, was the best fit to the data. From this analysis it is concluded that only increasing age and increasing year of study were associated with increased odds of having a database record of referral.

4.6 Discussion

4.6.1 Statement of principal findings

The GPRD was used to investigate the incidence, prevalence and management of people with a database record of venous, arterial and mixed venous arterial leg ulcers occurring during the period 2000 to 2006. Margolis et al.(2002) previously demonstrated that the GPRD was a valid source of data for the investigation of venous leg ulcers in people aged 65 years or greater. The current study expanded the investigation of the epidemiology of leg ulcers in the GPRD to all adults with leg ulcers with a database diagnosis of venous, arterial and mixed venous arterial. The current study also investigated the relationship between patient and practice level variables and reported leg ulcer management decisions.

Prevalence and Incidence

The results showed that over 97% of all incident and prevalent leg ulcer patients consulting in general practice had a database diagnosis of venous, the remainder documented as having arterial (approximately 2%), and a smaller proportion having mixed venous arterial leg ulcers (1%).

The relationship of gender, age and study year and the incidence and prevalence rates of the three database diagnoses of leg ulcers were explored using multiple regression models. Females had a higher risk of incidence and prevalence of venous leg ulcers (15% and 7%) whilst for arterial or mixed venous arterial leg ulcers no relationship with gender was observed. Older age was consistently associated with higher rates of all three database diagnoses of incident and prevalent leg ulcers examined ranging from an 8% to 12% increase in risk. Temporal differences in rates were also evident for all three database diagnoses of leg ulceration investigated. Incident venous and arterial leg ulcers were both shown to be decreasing throughout the study period (-3.4 to -6%). For prevalence, rates of venous leg ulcers were increasing (1.7%) whilst arterial leg ulcers showed no change. Both incident and prevalent rates of mixed venous arterial leg ulceration increased throughout the study period (12% and 10%). These results suggest that there is likely to be an increasing understanding of differential diagnoses of mixed venous arterial leg ulcers throughout the study period, which may be expected given the greater use of diagnostic assessment using ABPI in this patient group. The use of diagnostic assessment will be discussed in the next section which examines reported leg ulcer management.

Leg ulcer management

Three key areas of leg ulcer management were investigated; initial diagnostic assessment, initial provision of therapy and referrals. Few patients had a record of having received a diagnostic assessment consisting of ABPI measurement. Reported rates of assessment were 10.6% for those

diagnosed with venous leg ulceration, 12.0% for arterial leg ulceration and 21.8% for those patients diagnosed with mixed leg ulceration.

Multilevel logistic regression analyses were undertaken in the cohort of incident venous leg ulcer patients attending practices based in England to examine the relationship between a range of factors hypothesised to be associated with the odds of receiving a database record of an ABPI assessment. The results of these analyses demonstrated that being female (OR 0.86 95% C.I. 0.74-0.99), increasing year of age (OR 0.98 95% C.I. 0.97-0.99) and visiting a practice in the most deprived areas (OR 0.41 95% C.I.0.22-0.75) all were associated with reduced odds of having a record of receiving an ABPI assessment. These results clearly demonstrate that there were age, gender and socio-economic inequalities in diagnostic evaluations of leg ulcer patients that are receiving treatment in England. Increasing year of diagnosis was associated with a 1.04 increase in the odds of receiving ABPI assessment, indicating that the reported use of this test was slowly increasing over the study period. These results show that this increase was not equally distributed amongst all patients.

Records of reported therapies prescribed to patients in the first three months following diagnosis or in the month prior to diagnosis were examined. Irrespective of the leg ulcer diagnosis received, the leg ulcer treatments most commonly prescribed were bandages and dressings. Descriptive analyses revealed no differences in the types of therapies prescribed to patients by practice level deprivation.

With the exception of compression bandages and pentoxyfylline for the treatment of venous leg ulceration, treatments for other forms of leg ulceration are not well served by evidence of effectiveness (Jull et al. 2010; O'Meara et al. 2010). Throughout the study period 15.5% of venous leg ulcer patients had a database record of receiving a prescription for compression bandages, compared to 14.3% of arterial leg ulcer patients and 28.2% of mixed venous arterial leg ulcer patients. Examination of the reported rates of treatment or prescription of compression bandages throughout the study period showed no relationship between their usage and study year. Lower rates of the provision and prescriptions for compression therapy were observed in patients with a database diagnosis of arterial leg ulcers, which would be expected given the potential for harm of compression therapy in patients with significant peripheral arterial disease (RCN 2006). Despite the strong evidence for the use of pentoxyfylline it was found to be rarely prescribed to leg ulcer patients.

There were variations in the reported provision of leg ulcer therapy prescriptions to patients with different leg ulcer diagnoses. 73% of all venous leg ulcer patients had a database record of

receiving a prescription for a leg ulcer therapy, compared to 67.1% of arterial leg ulcer patients and 97.2% of patients with a diagnosis of mixed venous arterial leg ulcers. Database records provided no indication of why not all leg ulcer patients would have received a report of prescription for a wound therapy in the first three months following diagnosis, although several possibilities may exist. First, there is the possibility that treatments have been provided by other specialists to whom the patient has been referred. Second, multilevel logistic regression analysis using the cohort of patients with venous leg ulceration was undertaken. The results of this analysis indicated that only patient's age was associated with the odds of receiving a database record of a prescription for compression bandages. Third, there is the possibility that patients elected to self purchase compression bandages and did not therefore require a prescription. Although self purchase is possible, it is not thought to be common as the vast majority of the leg ulcer cohort are aged greater than 60 years and are entitled to free prescriptions on the NHS. Each increase in year of patient age was associated with a one per cent increase in the odds of having a database record of receiving treatment with, or a prescription for, compression therapy. Although ABPI measurement was shown to increase over the study period this was not found to be associated with any subsequent increase in the reported prescription of compression bandages for patients with a database diagnosis of venous leg ulcers.

Referral

Patients' records were searched for any database records of any referrals and leg ulcer specific referrals made in the year following incident diagnosis. The results showed that higher proportions of patients diagnosed with mixed venous arterial and arterial leg ulceration were referred for further specialist treatment, compared to those with patients diagnosed with venous ulceration. Once again, patients with a recorded diagnosis with arterial and mixed venous arterial leg ulceration were more likely to be referred than those with venous leg ulceration. The most common leg ulcer specialist treatment group that patients with all forms of leg ulceration were referred to was dermatology services. This indicates that referrals for leg ulcer patients emphasise wound treatment rather than treating the condition underlying the leg ulcer.

In patients diagnosed with venous leg ulceration, further exploration of covariates hypothesised to be associated with leg ulcer specific referrals were undertaken using logistic regression. Characteristics of the data meant that multilevel analysis could not be undertaken as the model would not converge. The only variable found to influence odds of referral to specialist leg ulcer practitioners was the year of diagnosis. Increasing year of diagnosis from the year 2000 was associated with a 14% increase in the odds of being referred over the study period. This result must be interpreted with caution as it may be biased due to the failure to account for practice level variation.

Finally, referrals to all providers were examined using multilevel analysis. In common with the earlier results examining leg ulcer specific referrals, year of diagnosis was also shown to be associated with an increase in the odds of having a record of receiving a referral although the effect was stronger increasing the odds of referral by 27%.

Of note was the finding that the reported rates of referrals to community nurses observed in this study were low, with less than one percent of all leg ulcer patients having a record of referral. It is unclear if these results are indicative of a change of management strategy or there are different referral pathways in operation which may mean that patients do not require a formal referral from general practice in order to access community nursing services.

4.6.2 Strengths and weaknesses of the current study

The work undertaken in this chapter has investigated factors hypothesised to contribute to the burden of the three commonly encountered forms of leg ulceration and the management of leg ulcers using one of the largest sources of primary care data available in the UK. The work is further strengthened by the fact that the case ascertainment strategy for venous leg ulceration has been previously validated in this same database achieving high levels of sensitivity and specificity (Margolis et al. 2002).

The current study has extended previously conducted analyses beyond descriptive epidemiological work, producing results that are more robust having been adjusted for multiple risk factors. There were however, some key explanatory variables that could not be included in these analyses which may limit the extrapolations that can be made from these results. The recording of factors that may contribute both to the aetiology and prognosis of the conditions underlying leg ulceration, such as obesity and smoking status, were not adequately reported for all patients and were therefore not used in any of the analyses. Of particular interest has been the finding that there are age, gender and practice deprivation based inequalities in the odds of receiving an assessment of ABPI using Doppler ultrasound.

There may be quite legitimate reasons why Doppler is not used within general practice but relevant information would not be reported or available from database records. As it is recommended that patients rest in the supine position for at least five minutes prior to measurement, there may be significant time pressures on staff that preclude its routine usage in primary care. An examination of consultation times by general practitioners conducted in several European countries found that mean consultation times in the UK were 9.4 minutes in length (Deveugele et al. 2002). Consultation times were not reported in the GPRD so the negative

influence of this factor can only hypothesised. Second, the results of other studies have suggested that there may be further impediments to the use of ABPI because of perceived or actual lack of expertise to carry out the test (Graham et al. 2003b). A third reason why this test may not have been used may relate to lack of availability of the device required to undertake the assessment. There is no data provided by the GPRD which would indicate whether a practice would have a Doppler machine, so this cannot be ruled out as a potential possibility beyond the low reported rates of usage. Fourth, there may also be concomitant clinical conditions which make the results of ABPI difficult to interpret. A common example of this problem may relate to patients with diabetes who may have calcified, non-compressible arteries may artificially inflate the value of the ABPI test (Jude 2004). The proportion of leg ulcer patients with diabetes was not evaluated, although earlier work conducted by Margolis et al. (2004b) has shown that at least 9% of patients aged greater than 65 years who developed venous leg ulcers had a historical record of diabetes. It is possible that patients' diabetic status may account for a proportion of the leg ulcer population not receiving ABPI assessment.

The relationship of many variables and patient relevant outcomes were examined using robust statistical methods including multilevel logistic models, in contrast to earlier findings which were limited to descriptive analysis. As such it has been possible to quantify the relationship between many hypothesised explanatory variables and patient management outcomes. A further limitation of this study, and indeed all studies conducted using general practice data are that the results are based on database records, which may contain some variations from actual clinical practice. Despite this potential limitation, all data used in the current study had met the GPRD requirement of being up to standard. Patients data is considered to be up to standard if details are internally consistent in four areas; age, sex, registration details and event recording (MHRA 2007).

A final limitation of the work conducted in this study is that has not been possible to explore the relationship between the reported management, and patient relevant outcomes such as healing. This is despite the availability of a Read code that would enable the status of wound healing to be reported in a patient's database record. Although not an explicit aim of this study to examine this, it was found that the Read code to indicate leg ulcer healing was infrequently if ever used for this cohort of leg ulcer patients. To address this limitation, further analysis will be conducted in a subsequent chapter using data from two recently completed clinical trials to examine the relationship between social factors and patient relevant events such as healing and adverse events.

4.6.3 Strengths and weaknesses of the current study in relation to other studies

The associations between female gender, higher age and increasing rates of leg ulceration concur with the results of epidemiological studies of the conditions that underlie leg ulceration as well as earlier studies of leg ulcer prevalence. Two of the common diseases that underlie leg ulceration, chronic venous disease and peripheral arterial disease are known to increase in incidence and prevalence as people age (Bergan et al. 2006). The majority of studies of chronic venous disease have reported higher prevalence rates in females compared males (Fowkes et al. 2001; Carpentier et al. 2004; Eberhardt &Raffetto 2005), although Evans (1999) reported higher rates in males.

The findings of this current study provide contradictory findings to an earlier incidence and prevalence study undertaken using a different version of the GPRD than that used in this study (Margolis et al. 2002). In their earlier study Margolis et al. (2002) found much higher incidence and prevalence rates of venous leg ulceration than were observed in the current study with rates shown to be at least 0.76 per 100 people in contrast to 0.09 per 100 people observed in the current study. In the previous chapter, analyses undertaken showed that the time period over which Margolis et al. (2002) conducted their study coincided with a unique set of circumstances. First, it was shown that the EPIC version of the GPRD that was used by Margolis et al. (2002) had the largest number of contributing practices and the largest number of person years available for analysis. Second, it was shown that the results of venous leg ulcers had peaked and were beginning to fall during this time period. As Margolis et al. (2002) had only reported the average incidence density rates over their study period of 1998 to 1996, the reduction in rates over the study period were not evident. The results observed in the current analysis clearly show that rates of venous leg ulceration in the GPRD have continued to fall throughout the years of the Margolis et al. (2002) analyses before stabilising from 2000 onwards. These results from 2000 onwards were used to conduct the current analyses. Finally the current analyses were results based on all patients aged 18 years and over compared to the population aged greater than 65 years studied by Margolis et al.(2002)

The results of this study demonstrated that many patient and practice level explanatory variables were associated with the reported care received by patients in practices that contributed to the GPRD. Gender, age and deprivation related inequalities in access to health care have been reported in many studies examining health service usage in the UK, but relationships with leg ulcer management have never been examined prior to the current analyses. The reported usage rates of ABPI and compression in this study were lower than in other relevant studies (Hickie et al. 1998; Schofield et al. 2000; Vowden &Vowden 2009)where half of people with leg ulcers were reported to have received an assessment of ABPI. However, rates from other studies leg ulcer management have in the main come from surveys of health professionals where the proportions

of respondents replying were low and no validation of the responses received were undertaken (Hickie et al. 1998; Graham et al. 2003b). The results of these studies were potentially hampered by non-response and recall bias. The responses obtained by the authors of these studies may represent responses of the most enthusiastic practitioners or within areas where leg ulcer treatment is seen as a priority, which may lead to an overly optimistic picture of current leg ulcer practice. With very few exceptions (Lorimer et al. 2003b; Clarke-Moloney et al. 2006), results from these studies were not validated against actual clinical records.

The results of the current analyses have shown that patients were provided with prescriptions or therapies constituting a wide variety of wound care treatments. Most commonly however patients were provided or prescribed bandages and dressings, which do not have high levels of evidence of effectiveness. In patients with venous leg ulceration, multilevel analysis suggested that older patients had a small but significant increase in the odds of having a database record of receiving compression bandaging. Whilst these results are encouraging, there is potential for harm if compression therapy is given without adequate assessment of leg ulcer circulation (Callam et al. 1987). No other studies examining leg ulcer management were found that have used any type of statistical analysis to make inferences to describe the likelihood of any aspect of patient management or referral.

Leg ulcer patients were referred to a wide variety of health professionals although the clinical reason for referral was not available from the patient's database records. It was perhaps unsurprising to see the results showing that patients with arterial and mixed venous arterial leg ulcers were more likely to be referred than patients with venous leg ulceration. It is likely that these patients may have been in poorer overall health. Results from other studies have shown that the low ABPI values seen in patients with these forms of leg ulceration is associated with high rates of morbidity and mortality, even after adjustment for age and sex (Heald et al. 2006). This is perhaps also further evidenced by the finding that arterial prevalence rates were decreasing over time compared to other database diagnoses of leg ulcers, which may suggest that mortality is high in this patient group. No other studies were located that examined referrals for leg ulcer patients from primary care therefore comparisons with other results is not possible.

The results obtained in the current study come from prospectively collected data from over 337 participating general practices that have previously been shown to be broadly representative of the UK primary care population (GPRD 2010). To date, these analyses represent the largest study of leg ulcer management yet undertaken in the UK although it is recognised that the results of management have come from English practices limits the generalisability of these findings.

4.6.4 Meaning of the study

The results of this study confirm previous exploration of factors shown to contribute to the burden of disease of leg ulceration. Female gender and older age were both shown to be associated with higher rates of leg ulceration for the majority all though not all leg ulcer patients. Of particular note was the finding that gender had no relationship with arterial leg ulcer burden.

The results presented in this chapter have further highlighted that non-venous leg ulcers are rare, although the findings from this study also caution against accepting the findings of the distribution of leg ulcer pathology from database diagnostic records. This is particularly in light of the finding that there are low levels of patients that are having measures to quantify leg ulcer circulation, such as ABPI measurement, which may indicate some degree of error in the assignment of pathological classifications given to patients.

These results provide further evidence that implementation of guideline-based care for patients with leg ulceration remains sub-optimal, although regression models provide evidence that improvements in practice are occurring over time, albeit slowly and not equally amongst all patients of different gender, ages and socio-economic circumstances.

5.0 Investigation of the effect of deprivation on the burden of and management of leg ulcers.

5.1 Introduction

The results of the previous chapter, using the GPRD, demonstrated that many advances in the understanding of leg ulcer distribution and management could be achieved using general practice data. However, only a limited exploration of the role of socio-economic factors could be undertaken using the GPRD as no information about the patients' socio-economic position was available. Whilst socio-economic associations with some aspects of leg ulcer management were observed with practice level deprivation, it remains unclear whether these same associations would be observed for individual markers of socio-economic position.

A central tenet of the NHS is that care for all should be provided according to need and not ability to pay and that the NHS will work to keep people healthy and work to reduce health inequalities (Department of Health 2003). Despite these policies it has been asserted that '*although people from low socio-economic backgrounds and with poor health use comparatively more primary-care services (which accords with their increased need for care), they are no more likely to be prescribed medication, are less likely to be referred for elective outpatient treatment, and have lower rates of elective surgery in relation to need*' (Raine &McIvor 2006).

The identification and reduction of health inequalities remain key policy objectives of both the UK government and the NHS. Quantification of risk factors for the development of leg ulcers will be useful for designing preventative programmes and ensuring that sub-groups in the population with the greatest need for services can be targeted. Furthermore, by identifying where current clinical practice may be suboptimal; this study will provide useful evidence for targeted quality improvement interventions in primary care.

No data related to the socio-economic position of an individual are routinely recorded during interactions with the health service. Some examples of individual measures of socio-economic position include income, occupation and level of educational attainment. Pragmatically, therefore, many health researchers examining health inequalities used area based measures of deprivation as a proxy for measurement of individual socio-economic position. This is because these can be calculated using routinely available information such as the patient's or the practice's postcode. Some examples of area level measures include the Index of Multiple Deprivation and the Townsend Material deprivation index. These area based deprivation measures are both derived

using a composite of routinely collected data from sources such as census and other government data.

In the previous study no socio-economic information was available at the denominator level of either person time or number of eligible patients per year. This meant that exploration of the effect of socio-economic position on the distribution and management of leg ulceration could not be conducted. In order to examine the association between an individual's socio-economic position and the distribution, management and referral decisions for patients treated for leg ulceration in general practice another source of data was required.

The data source which will be used to examine the effect of socio-economic factors on the pathology, distribution, management and referral decisions for patients with leg ulceration in general practice is the THIN database. The THIN database was chosen as it contains a measure of the Townsend deprivation index for each patient attending a practice contributing to the database, a proxy measure of individual socio-economic position. Unlike the earlier study using the GPRD, these data were provided at the patient rather than practice level variable. As practice level deprivation is not available from the THIN database, it will not be evaluated in these analyses.

The methods used to both identify and calculate the incidence and prevalence of leg ulcers of venous, arterial and mixed ulceration in the THIN database were fully described in chapter three. From the results of analyses conducted in chapter three it was concluded that the results from 2000 onwards produced the most reliable results of incidence and from 2001 onwards for prevalence for the GPRD and THIN databases.

To ensure comparability between the results produced in the current chapter and those produced in chapter four, analyses is restricted to the examination of incident leg cases diagnosed from 2000 to 2006 and prevalent leg ulcer cases diagnosed from 2001 to 2006. In addition these analyses are restricted to people with a database diagnosis of venous, arterial and mixed venous leg ulcers. All analyses are adjusted for the same explanatory variables as were included in the previous chapter's analyses; these variables being age, sex and study year. Full details of the scientific justification of the inclusion of these variables in the analyses can be found in the previous chapter. A further variable available in the THIN database, practice list size, is also included in the analyses examining leg ulcer management. Practice list size is included in the analyses as previous research has shown that there are negative impacts of the care of heart disease and diabetes received in general practice associated with smaller practice list size (Millett et al. 2007; Saxena et al. 2007). This aspect of care provision has never been examined in leg ulcer

patients and is worthy of exploration given the evidence from the treatment of other disease areas. The overall aim of this current analysis is to examine the relationship between patient level socio-economic position and the diagnostic classification, distribution, management and referral decisions for leg ulcer patients within U.K. general practice.

5.2 Research Questions

This analysis undertaken in this chapter will attempt to answer the following research questions;

i) Do the prevalence and incidence of leg ulceration vary by socio-economic position?

ii) Does the initial assessment or management of patients vary by patients' socio-economic position?

iii) Does the nature of referrals for the provision of leg ulcer treatments vary by patients' socio-economic position?

5.3 Methods

It is the intention to replicate the methods used to conduct the previous analyses using the GPRD in chapter four. Where the methods used are identical to those used in the previous chapters study, reference is made to the previous chapter's methods section to avoid repetition. Any additional methods that are unique to this chapter's study are described in full.

In this chapter the results of incidence and prevalence of leg ulceration, calculated previously in chapter three, are further explored to examine the effect of social deprivation. The method used to calculate social deprivation measure provided by the THIN database is described below.

5.3.1 Method for calculation of the social deprivation measure

The socio-economic information available for each patient in the THIN databases is the Townsend deprivation index, a measure of material deprivation calculated using census data and linked to area of residence. The Townsend deprivation index (Townsend et al. 1988) is calculated using the following domains; unemployment, car ownership, home ownership and overcrowding. It has been used extensively in UK based studies to examine relationships between deprivation and health. These domains were obtained from the 2001 census data and linked to a person's residence using their postcode data. In order to maintain patient anonymity the Townsend deprivation score is calculated by the THIN database administrators. These raw Townsend scores were then converted into fifth rank for use by external researchers accessing the THIN database.

In some cases the deprivation fifth rank for a patient changed during the study period, due to a change in residence. If this was the case, the most recent deprivation fifth rank was used in all

calculations. This same method was applied by the database administrators when calculating the denominator data by deprivation fifth rank. A fifth rank of one corresponded to the least deprived areas and a fifth rank of five to the most deprived areas. By providing the score as a rank, the potential for individual patients being inadvertently identified is minimised.

5.3.2 Methods for the exploration of the effect of explanatory variables on incidence and prevalence rates

First, graphs were produced to examine the stratified effect of gender and Townsend deprivation fifth rank on incidence and prevalence rates of the three forms of leg ulcers examined.

Second, Poisson regression was used to explore the effect of explanatory variables, which included age, gender, study year and Townsend deprivation fifth rank, on incidence and prevalence rates. '*Poisson regression is the standard method used to model count response data*' (Hilbe 2008). Likelihood ratio tests were undertaken to examine any deviations from the Poisson distribution. If there was evidence of over-dispersion of nonzero counts relative to the Poisson distribution, a negative binomial regression approach was employed (Byers et al. 2003). Separate models were undertaken to examine the effect of explanatory variables on the incidence of database diagnoses of venous, arterial and mixed leg ulceration.

It is important to examine both incidence and prevalence to evaluate the causal relationship between leg ulcers and socio-economic position. Existing evidence shows that socio-economic factors may be associated with prevalent leg ulcers but there are no previous studies that have examined their relationship with incidence and thus the causal pathway remains unclear.

5.3.3 Methods for the exploration of initial assessment

Recommendations from all three UK guidelines for the management of leg ulcers concluded that all leg ulcer patients should be assessed using Doppler ultrasound aided measurement (CREST 1998; SIGN 1998; RCN 2006). This assessment determines whether the arterial supply to the lower legs is impaired by arterial disease using Doppler ultrasound and the patient's ankle brachial pressure index can be calculated. Values calculated from this measurement can, along with other clinical history and observation, be used to guide appropriate management decisions.

Database records of ankle brachial pressure index measurements were sought using the same temporal parameters as applied in chapter four. Records indicative of any measurement of ABPI in the 30 days prior or in the 90 days post incident diagnosis were sought. A full description of the justification for this time period can be found in section 4.4.2 of chapter four. In the THIN

database, records of ABPI measurement were located by searching for relevant Read and diagnostic codes. The codes used to identify these events can be supplied upon request.

Frequencies and proportions of patients with a database record of receiving ABPI assessment were produced to examine variations over time and by database diagnoses of leg ulceration. The results of these descriptive analyses were stratified by study year and database diagnosis of leg ulceration. A second descriptive analysis was undertaken to examine the proportion of incident venous leg ulcer patients within each practice who had a record of receiving ABPI assessment.

Finally, multilevel models were used to examine the statistical relationship between both patient and practice level variables and the odds of receiving an ABPI assessment. As the outcome variable was binary, you had a record of receiving ABPI assessment or not, multilevel logistic regression analyses were undertaken.

5.3.4 Methods for the exploration of initial therapeutic management

To replicate the methods used in chapter four, records of leg ulcer patients in the THIN database were searched for records of the prescription of any leg ulcer therapy throughout the study period.

The same criteria were applied to the selection of leg ulcer therapies for analysis as were used in the previous chapters study. A full description of these selection criteria can be found in chapter four in section 4.4.3.

In the THIN database, prescriptions or application of these products were coded using a variety of methods. These included Read codes, BNF chapter and subchapter headings and records made using the brand or generic product names referred to in the database as multilex product codes. The codes used to identify records of prescription of these leg ulcer therapies in the THIN database can be supplied upon request.

Four descriptive analyses were undertaken. The first descriptive analysis was undertaken to examine the full range of therapies prescribed and to examine any variations over time and by leg ulcer diagnosis. These frequencies and proportions of therapies prescribed are presented stratified by database diagnosis of leg ulceration and study year. Second, the association between deprivation fifth rank and leg ulcer prescription type was examined in the cohort of patients diagnosed with venous leg ulceration. The third descriptive analyses examined the relationship between the year of study and the proportion of patients receiving a prescription for compression therapy. A fourth and final descriptive analysis was undertaken to examine the

proportion of incident venous leg ulcer patients within each practice who had a record of receiving compression therapy.

Compression therapy was of particular interest as it is one of the few leg ulcer therapies with strong evidence of effectiveness and it was recommended by all three UK leg ulcer guidelines for the treatment of venous leg ulceration (CREST 1998; SIGN 1998; RCN 2006).

Multilevel analyses were then performed to determine if any patient or practice level variables were statistically associated with receiving a prescription for compression therapy. Once again the outcome of this analysis was binary, you were prescribed compression or you were not, so multilevel logistic regression analyses were undertaken.

5.3.5 Methods for the exploration of initial referral decisions

Referral decisions made by primary care providers for leg ulcer care have not been comprehensively explored in the UK. Guidelines for the management of leg ulceration were not well served by evidence to provide specific recommendations as to who or when patients should be referred (CREST 1998; SIGN 1998; RCN 2006). There are many examples of primary care trusts developing their own referral care pathways to specialist leg ulcer services depending upon their needs and budgets (Preston Primary Care Trust 2006; South Birminham Primary care trust 2006). No studies were found that examined patient outcomes following a referral from general practice to other health care practitioners or services.

To replicate the methods of the study in chapter four, referrals were again examined in three stages and restricted to exploration of referrals taking place in the year following incident diagnosis. First, a descriptive analysis of the entire range of health and social care professionals that leg ulcer patients were referred to was undertaken and results were stratified by leg ulcer diagnosis . Second, referrals to health professionals who provide specialist treatment for persons with leg ulcers were examined. Referrals were considered to be leg ulcer related if they were referrals to one of the following health practitioners or clinic settings, vascular surgeons, podiatrists, dermatology services, leg ulcer clinics or pain clinics. The frequencies and proportions of patients referred to these clinical practitioners were calculated. Separate descriptive analyses were performed for patients with each of the three database diagnoses of leg ulceration examined. A final descriptive analysis was undertaken to examine the proportion of incident venous leg ulcer patients within each practice who had a record of being referred for specialist leg ulcer treatment. The exact code list of all referrals searched for using the THIN database can be provided upon request.

Third, multilevel models were developed to examine the relationship between patient and practice level variables; and the outcome variable of receiving any type of specialist leg ulcer referral in year following diagnosis. Once again the outcome of this analysis was binary, patients were referred or they were they were not, so multilevel logistic regression analyses were used to analyse the data.

Potential correlates of receiving a referral for further leg ulcer assessment and therapy were selected by both reviewing the literature and by their availability in the THIN database. These were then grouped into individual and practice level variables.

For all three multilevel models examining the diagnosis, treatment and referrals of leg ulcer patients; the individual and practice level variables that were selected for inclusion in the model were; age, gender, study year, Townsend deprivation fifth rank of the patient and practice list size.

The results of all statistical tests were assumed to be statistically significant when p value was less than or equal to 0.05. Confidence intervals of point estimates will also be reported.

Some concern has been voiced in the literature regarding the high susceptibility to bias of multilevel logistic models if there are fewer than five participants in any group (Moineddin et al. 2007; Theall et al. 2008). If this was the case in any of our analyses, multilevel logistic analyses were not performed.

A range of different models were fitted to the data, exploring the role of patients and practice level variables in turn. Model selection was determined by calculation of the Akaike's Information Criterion (AIC). *"AIC is the sum of the deviance and two times the number of parameters in the model so that the better fit is balanced by the increased complexity of a larger model"* (Sellström et al. 2003). As per the previous chapters analyses, best model fit selection was considered to be the model with the smallest AIC value.

5.4 Results

5.4.1 Summary characteristics of the prevalent cohort

The THIN database was searched for adults with a record of prevalent leg ulceration occurring during the study period of January 2001 to December 2006. Over 17,000 patients were found to have consulted with leg ulcers during the study period. The details of the prevalent cohort are shown below in table 5.2. The majority of leg ulcer patients had venous ulcers (94.1%), followed by arterial (3.4%) and mixed venous-arterial (2.0%). Irrespective of the database diagnosis of leg ulceration examined, more females than males had prevalent leg ulceration and a smaller proportion of all leg ulcer patients were located in the most deprived fifth, relative to other fifths. Patients with prevalent leg ulceration were most commonly found in the older ages of the population, with some variation by leg ulcer classification. The results showing the baseline characteristics of the prevalent cohort stratified by database diagnosis of leg ulceration are shown below in table 5.1.

Table 5.1 Baseline characteristics of the prevalent cohort in the THIN database 2001 to 2006 stratified by leg ulcer diagnosis

Ulcer type	Venous Ulcers	Arterial Ulcers	Mixed Venous-Arterial Ulcers
N (% of overall total)	16,500 (94.6)	591 (3.4)	349 (2.0)
Female, N (%)	10307 (62.5)	347 (58.5)	233 (66.8)
Mean age (SD), Median, range, in years	74.3 (14.2) 77, 18-109	78.0 (11.4) 80, 21-103	78.7 (11.2) 81, 38-104
Townsend deprivation fifth, N(%)			
1 (least deprived)	3172 (19.2)	111 (18.7)	66 (18.9)
2	3303 (20.0)	122 (20.5)	76 (21.8)
3	3419 (20.7)	117 (19.7)	87 (24.9)
4	3153 (19.1)	117 (19.7)	56 (16.0)
5 (most deprived)	2375 (14.4)	82 (13.8)	42 (12.1)
Missing	1078 (6.5)	46 (7.7)	22 (6.3)

5.4.2 Results of the average annual period prevalence of leg ulceration stratified by deprivation and gender

First, average annual period prevalence rates for men and women, stratified by deprivation fifth rank are presented. These results are presented first for venous followed by arterial and then mixed venous arterial leg ulceration.

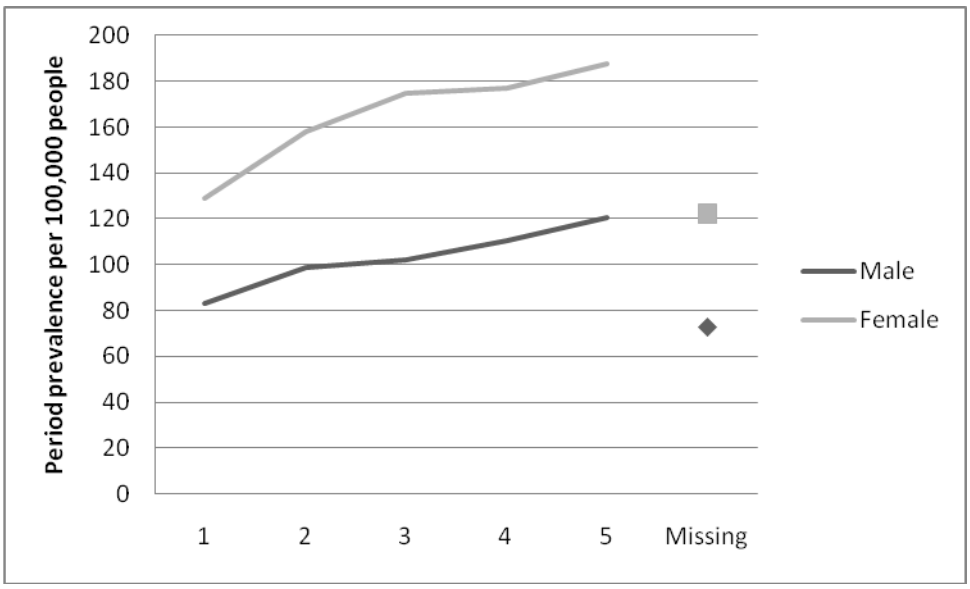

Figure 5.1 Average annual period prevalence rate of venous leg ulceration in the THIN database for the years 2001 to 2006, stratified by gender and deprivation fifth rank

Figure 5.1 above shows the average annual period prevalence rate of venous leg ulceration, stratified by gender and deprivation fifth rank for the years 2001 to 2006. Prevalence rates of venous leg ulceration were shown to increase with Townsend deprivation fifth rank, indicating areas with higher levels of deprivation for both genders. Prevalence rates for women were 40% higher than those observed in men, irrespective of the deprivation fifth rank examined. Period prevalence ranged from a low of 72.9 per 100,000 males, for those with a missing deprivation fifth rank, to a high of 187.9 per 100,000 women for those living in an area with a deprivation fifth rank five which are areas with the highest levels of deprivation.

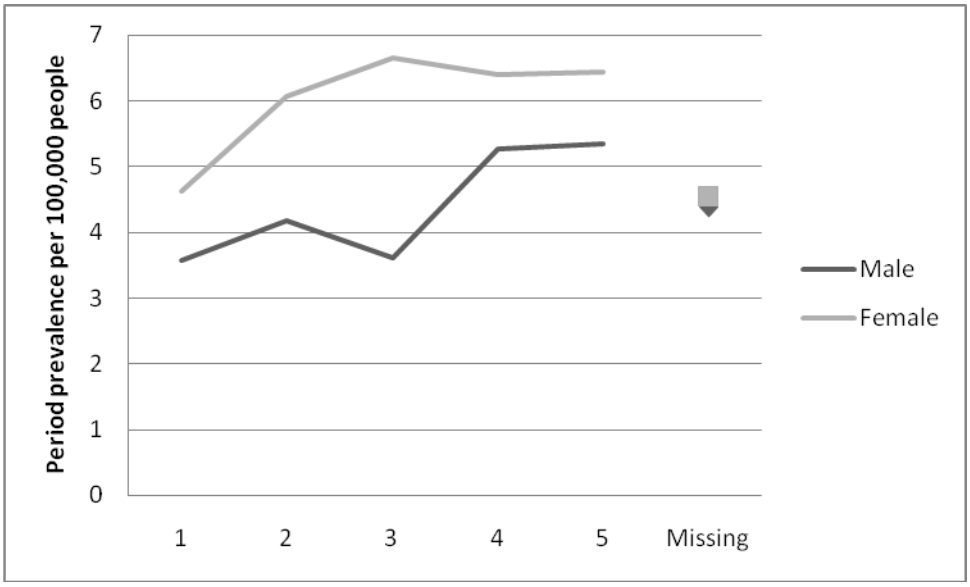

Figure 5.2 Average annual period prevalence rate of arterial leg ulceration in the THIN database for the years 2001 to 2006, stratified by gender and deprivation fifth rank

Next, the period prevalence rates of arterial leg ulceration were calculated and stratified by gender and deprivation fifth. Period prevalence rates of arterial leg ulceration were higher in females than males across all deprivation fifth ranks (seen above in figure 5.2). However, no consistent relationship was observed between deprivation fifth rank and prevalence in either males or females. Average annual period prevalence rates ranged from a low of 3.6 per 100,000 persons in males living in the least deprived fifth rank of one to a high of 6.6 per 100,000 persons in females living in areas with a fifth rank of three which is an area of average deprivation.

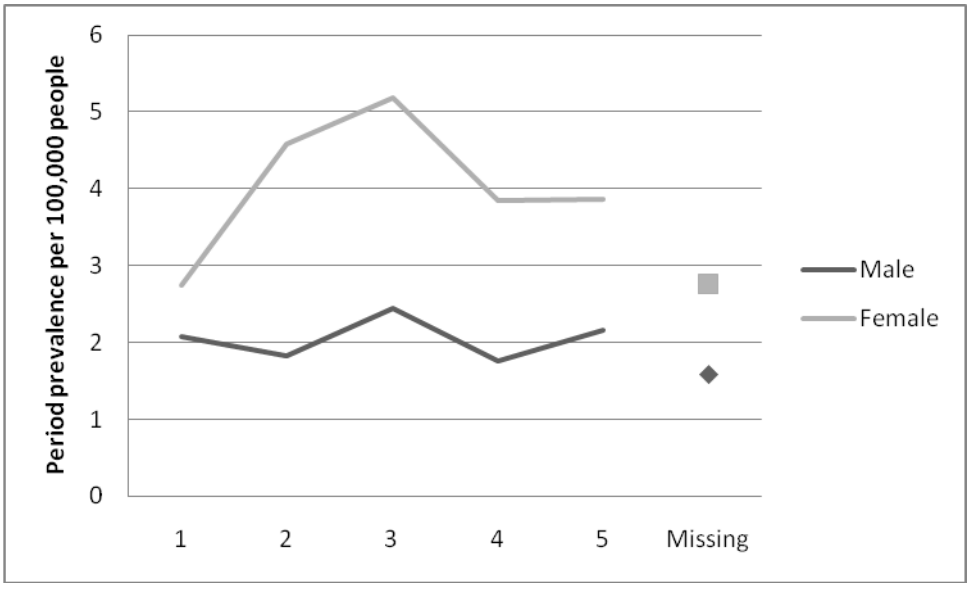

Figure 5.3 Average annual period prevalence rate of mixed venous-arterial leg ulceration in the THIN database for the years 2001 to 2006, stratified by gender and deprivation fifth

Finally, average annual period prevalence rates of mixed venous-arterial leg ulceration were calculated. The results of these calculations, stratified by gender and deprivation fifth rank, are shown above in figure 5.3. Consistent gradients between average annual period prevalence rates of mixed venous-arterial leg ulceration and deprivation fifth rank were not observed. Consistent with the other forms of leg ulceration examined, average annual period prevalence rates of mixed venous-arterial leg ulceration were higher in women than men. Rates ranged from a low of 1.6 per 100,000 men those living in areas of with a missing deprivation fifth rank to a high of 5.2 per 100,000 women for those living in an area with a deprivation fifth rank of three which corresponds to an area of average deprivation.

5.4.3 Results of the examination of prevalence rates using negative binomial and/or Poisson regression

Regression analysis were undertaken in order in examine whether socio-economic differences were still evident when other variables known to affect rates were adjusted for. The type of regression analyses undertaken were either negative binomial regression or Poisson regression depending on the distribution of the data. Explanatory variables hypothesised to affect prevalence rates were included in the analysis. These variables were age, gender, Townsend deprivation fifth rank and study year. The results of these analyses are shown firstly for venous leg ulcer patients, then for arterial and mixed venous-arterial leg ulcer patients. The results of these analyses are based on prevalent patients with complete data. The results, therefore do not include data from 6.5% of venous, 7.7% of arterial and 6.3% of mixed venous arterial leg ulcer patients for whom Townsend fifth deprivation rank was not available.

Table 5.2 Exploration of the effect of variables on the prevalence rate ratios of venous leg ulceration

Characteristic	Prevalence RR (95% C.I.)	p-value
Age (year)	1.083 (1.081, 1.084)	<0.001
Gender		
Male	1	
Female	1.142 (1.100, 1.186)	
Townsend deprivation fifth rank		
1 (low deprivation)	1	
2	1.101 (1.042, 1.165)	<0.001
3	1.250 (1.182, 1.321)	<0.001
4	1.309 (1.237, 1.386)	<0.001
5 (high deprivation)	1.480 (1.393, 1.573)	<0.001
Study year		
1 year increase	1.037 (1.026, 1.048)	<0.001

$\chi 2$ 7, 5362=8207.45, P<0.001, pseudo R2=0.34, α for dispersion 0.04 (95% confidence interval 0.03-0.05)
RR rate ratio CI confidence interval

Negative binomial regression was used to examine the effect of age, gender, Townsend deprivation fifth rank and study year on the prevalence rate ratios of venous leg ulcers. As can be seen above in table 5.2, several co-variates were shown to be statistically significantly associated with increases in average annual venous leg ulcer period prevalence. Specifically, increasing year of age (8% increase), female gender (14% compared to men), increasing year of diagnosis (3.7%) and increasing deprivation fifth rank all showed a positive relationship with higher prevalence rates. Prevalence rates were shown to rise by approximately 10 % for each increase in Townsend deprivation fifth rank from fifth one.

Poisson regression was then undertaken to examine the effect of the same explanatory variables on the risk of prevalent arterial leg ulceration. The results of these analyses are shown below in table 5.3.

Table 5.3 Exploration of the effect of variables on the prevalence rate ratios of arterial leg ulceration

Characteristic	Prevalence RR (95% C.I.)	p-value
Age (year)	1.108 (1.100, 1.115)	<0.001
Gender		
Male	1	
Female	0.904 (0.761, 1.076)	0.257
Townsend deprivation fifth rank		
1 (least deprived)	1	
2	1.110 (0.858, 1.435)	0.428
3	1.161 (0.895, 1.505)	0.259
4	1.305 (1.006, 1.692)	0.045
5 (most deprived)	1.372 (1.031, 1.825)	0.030
Study year		
1 year increase	1.054 (1.003, 1.107)	0.037

χ2 7, 5362=1465.12, P<0.001, pseudo R2=0.34, Goodness of fit test χ2 1861.03 P=1.00
RR rate ratio CI confidence interval

Variables positively associated with higher prevalence rates of arterial leg ulceration were age, deprivation fifth rank and study year. Increasing year of age (10.8%), membership of deprivation fifth ranks four and five (>30%) and increasing year of study (5%) were all associated with a higher risk of prevalence.

Although deprivation was linked to prevalence, it was only statistically significant for persons living in the most deprived fifth ranks, four and five. A test for linear trend of deprivation rank effect on prevalence rate ratios showed that there was a 10% increase in prevalence rate ratios with each increasing deprivation rank (prevalence rate ratio 1.101, 95% CI 1.044-1.161 p<0.001). Although female gender was shown to be associated with lower prevalence rate ratios of arterial leg ulceration compared to men (0.884) this relationship was not found to be statistically significant (p=0.257).

Poisson regression was then used to examine the cohort of patients with prevalent mixed venous arterial leg ulceration and the results of this analysis can be seen above in table 5.4 below.

Table 5.4 Exploration of the effect of variables on the prevalence rate ratios of mixed venous arterial leg ulcers

Characteristic	Prevalence RR (95% CI)	p-value
Age (years)	1.108 (1.099, 1.118)	<0.001
Gender		
Male	1	
Female	1.272 (1.007, 1.608)	0.044
Townsend deprivation fifth rank		
1 (least deprived)	1	
2	1.175 (0.845, 1.634)	0.338
3	1.448 (1.051, 1.995)	0.024
4	1.053 (0.737, 1.505)	0.776
5 (most deprived)	1.175 (0.798, 1.731)	0.415
Study year		
1 year increase	1.109 (1.040, 1.183)	0.002

χ2 7, 5362 =915.77, P<0.001, pseudo R2=0.32, Goodness of fit test χ2 1364.16 P=1.00
RR rate ratio CI confidence interval

Each increasing year of age (10.8%), membership of deprivation fifth ranks three (44.8%) and increasing year of study (10.9%) were all shown to be associated with an increased risk of prevalence. Although deprivation was linked to prevalence this was only statistically significant for persons living in area of fifth rank three. Neither gender (prevalence rate ratio 1.202 p=0.084) nor test for trend of deprivation (prevalence rate ratio 1.060; p=0.115) were found to have a statistically significant relationship with mixed venous arterial leg ulceration prevalence.

5.4.4 Summary characteristics of the incident cohort

A search of the THIN database from January 2000 to December 2006 identified over 15,000 patients who met the criteria as having incident venous, arterial or mixed venous arterial leg ulcers. The baseline characteristics of the patients are shown in table 5.5 below. Most incident patients had a database diagnosis of venous leg ulcers (95.2%), with arterial and mixed venous arterial leg ulcers making up the remaining 4%. For all three diagnoses of leg ulceration examined, women comprised the highest proportion of incident cases, and mean and median ages of all patients were in excess of 73 years. For all three database diagnoses of leg ulcers examined, patients living in the most deprived fifth rank (5) formed the smallest proportion of all leg ulcer patients with a valid Townsend deprivation fifth rank.

Table 5.5 Baseline characteristics of the incident cohort in the THIN database 2000 to 2006, by ulcer pathology

Ulcer type	Venous Ulcers	Arterial Ulcers	Mixed Venous/ Arterial Ulcers
N (% of overall total)	14,568 (95.2)	479 (3.1)	244 (1.7)
Female, N (%)	9,158 (62.9)	281 (58.7)	170 (69.7)
Mean age (SD), Median range, in years	73.7 (14.4) 77, 18-109	78.0 (11.5) 80, 21-103	78.7 (11.2) 81, 39-104
Townsend deprivation fifth rank, N (%) 1 (least deprived) 2 3 4 5 (most deprived) Missing	 2802 (19.2) 2871 (19.7) 3060 (21.0) 2796 (19.2) 2065 (14.2) 974 (6.7)	 97 (20.3) 99 (20.7) 86 (18.0) 90 (18.8) 71 (14.7) 36 (7.5)	 46 (18.9) 53 (21.7) 56 (23.0) 46 (18.9) 31 (12.7) 12 (4.9)

5.4.5 Results of the average incidence density rates of leg ulceration stratified by Townsend deprivation fifth rank and gender

Descriptive analyses are presented which show the relationship between deprivation and gender. First, shown below in Figure 5.4 are the results for venous leg ulceration.

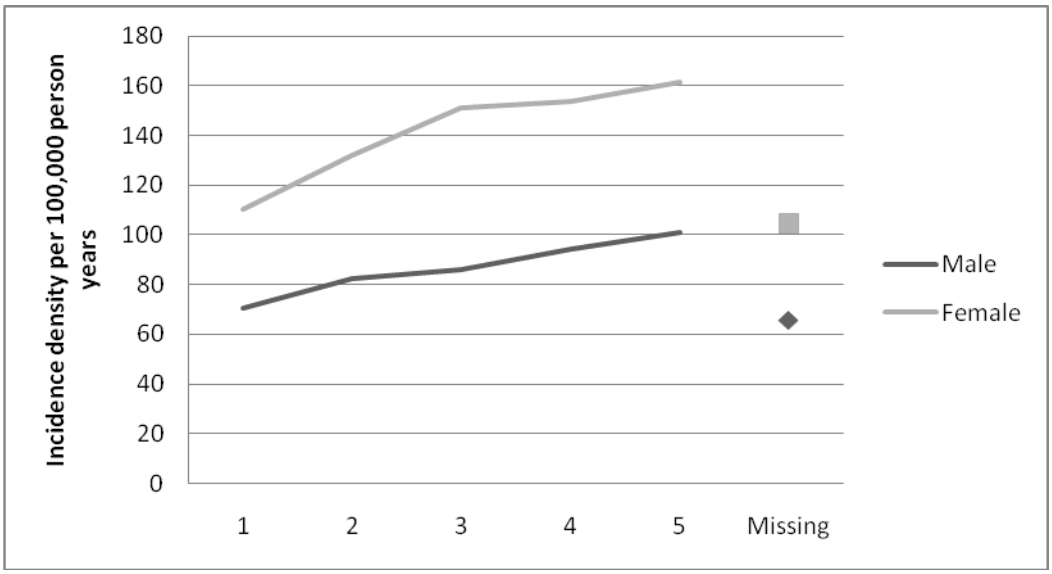

Figure 5.4 Average incidence density rate of venous leg ulceration, stratified by gender and deprivation fifth rank for the years 2000 to 2006

Rates of incident venous leg ulceration were highest amongst people living in areas of high deprivation. This association was consistently observed in the results for both genders. Females had the highest rates of venous leg ulceration within each deprivation fifth, which within most fifths was approximately double the rates for males. Rates ranged from 70.5 per 100,000 person years in the lowest deprivation fifth for males, to a high of 161.3 per 100,000 person years in females in the most deprived fifth rank of five.

Next incidence density rates of arterial leg ulceration stratified by gender and Townsend deprivation fifth rank were calculated and shown in figure 5.5 below.

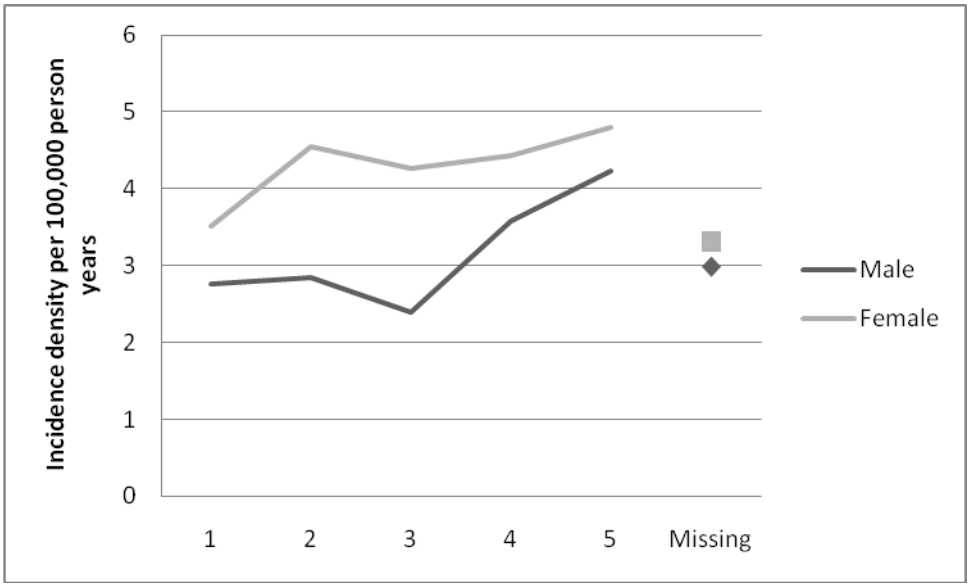

Figure 5.5 Average incidence density rate of arterial leg ulceration, stratified by gender and deprivation fifth for the years 2000 to 2006

These results indicated that incidence density rates of arterial leg ulceration were highest in females and males who lived in the most deprived fifths. Incidence density rates of arterial leg ulceration were higher for females than males within each deprivation fifth. The smallest differences in the rates between genders were observed in fifths one and five. Incidence density rates ranged from 2.4 per 100,000 person years in males living in area of medium deprivation corresponding to a rank of three to a high of 4.8 per 100,000 person years, for females living in areas of highest deprivation, which corresponds to a fifth rank of five.

Lastly, incidence density rates of mixed venous-arterial leg ulceration were calculated. Figure 5.6 below shows the results stratified by gender and deprivation fifth rank.

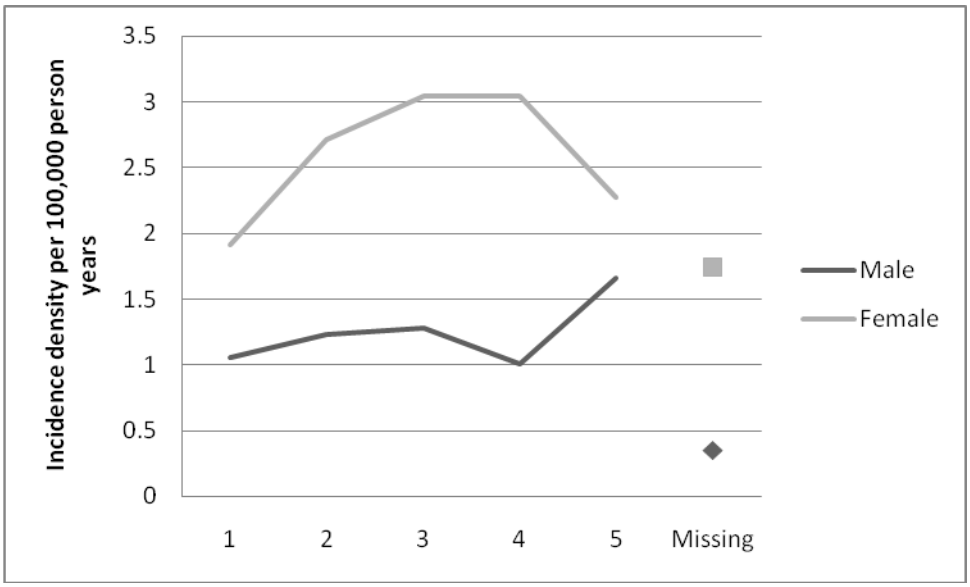

Figure 5.6 Average incidence density rate of mixed venous/arterial leg ulceration, stratified by gender and deprivation fifth rank for the years 2000 to 2006

Females were found to have the highest incidence density rates of mixed venous arterial leg ulcers within each deprivation fifth. Rates for females were at least double those for males. No clear gradient of incidence density rates of mixed venous arterial leg ulcers and deprivation was observed in the results for either gender. Rates were shown to vary from a low of 0.35 per 100,000 person years for males living in areas where the deprivation rank was missing to a high of 3 per 100,000 person years for females living in areas with deprivation fifth ranks of three or four.

5.4.6 Results of the examination of incidence density rates using negative binomial and/or Poisson regression

Regression analysis was undertaken to determine whether socio-economic differences existed in the incidence density rates of leg ulceration when adjusted for age, gender and year of study. The type of regression undertaken was either negative binomial regression or Poisson regression as appropriate to the data. The results of these analyses are shown firstly for incident venous leg ulcer

patients then arterial and mixed leg ulcer patients. These results were based on patients for whom complete information was available and so does not include the 6.7% of venous, the 7.5% of arterial, nor the 4.9% of mixed venous arterial leg ulcer patients for whom Townsend deprivation fifth rank information was missing.

Negative binomial regression was used to examine variables hypothesised to influence incidence density of venous leg ulceration. The results of this analysis are shown below in table 5.6.

Table 5.6 Exploration of the effect of variables on the incidence rate ratios of venous leg ulceration

Characteristic	Incidence RR (95% CI)	p-value
Age (years)	1.081 (1.079-1.082)	<0.001
Gender		
Male	1	
Female	1.170 (1.127-1.215)	<0.001
Townsend deprivation fifth rank		
1 (low deprivation)	1	
2	1.075 (1.017-1.137)	<0.001
3	1.243 (1.177, 1.314)	<0.001
4	1.304 (1.232-1.379)	<0.001
5 (high deprivation)	1.442 (1.357-1.532)	<0.001
Study year		
1 year increase	1.003 (0.994-1.012)	0.504

χ2 7, 6323=8700.45, P<0.001, pseudo R2=0.34, α for dispersion 0.03 (95% C.I. 0.02-0.05)
RR rate ratio CI confidence interval

Patient's age, gender and Townsend deprivation fifth ranks were shown to have a statistically significant relationship with incident rate ratios of venous leg ulcers. Each increasing year of age increased rate ratios by 8.1 % (95% C.I. 7.9-8.2), being female increased rate ratios by 17 % (95% C.I. 12.7-21.5) and living in an area with a deprivation fifth rank higher than one were all associated with higher rate ratios of venous leg ulceration. With each increase in deprivation fifth rank, rate ratios of venous leg ulceration were shown to increase by approximately 10%. Finally, the results indicated that there were no statistically significant increases or decreases in incident venous leg ulceration throughout the study period. No relationship with study year was observed.

Poisson regression was then used to examine the relationship between explanatory variables and the incidence density rate ratios of arterial leg ulceration. The results from this analysis is shown below in table 5.7

Table 5.7 Exploration of the effect of explanatory variables on the incidence rate ratios of arterial leg ulceration

Characteristic	Incidence RR (95 % CI)	p-value
Age (years)	1.109 (1.101-1.117)	<0.001
Gender		
Male	1	
Female	0.899 (0.743-1.050)	0.159
Townsend deprivation fifth rank		
1 (low deprivation)	1	
2	1.044 (0.789- 1.381)	0.765
3	0.977 (0.730- 1.306)	0.874
4	1.157 (0.867- 1.542)	0.321
5 (high deprivation)	1.354 (0.996- 1.840)	0.053
Study year		
1 year increase	1.067 (1.018- 1.119)	0.007

χ2 7, 13485=1594.01, P<0.001, pseudo R2=0.31, Goodness of fit test χ2 2458.08 P=1.00
RR rate ratio CI confidence interval

For incident arterial leg ulcers, age and year of diagnosis showed a statistically significant relationship with incidence. Each increasing year of age and increasing year of diagnosis were associated with increasing incidence rate ratios of arterial leg ulceration. A test for trend of Townsend deprivation fifth rank showed a six per cent increase in the average annual incidence density rate ratio for each increase in Townsend deprivation fifth rank above however, this estimate was not statistically significant (p=0.059). Although the value for the incident rate ratio showed that females had an 10.1% reduction in the risk of developing arterial leg ulcers compared to males this was not statistically significant (p=0.159)

Finally, Poisson regression was used to examine the influence of explanatory variables on the rate ratios of incident mixed venous arterial leg ulceration. The results of this analysis are shown below in table 5.8.

Table 5.8 Exploration of the effect of explanatory variables on the incidence rate ratios of mixed venous-arterial leg ulceration

Characteristic	Incidence RR (95% CI)	p-value
Age (years)	1.107 (1.096- 1.118)	<0.0001
Gender		
Male	1	
Female	1.389 (1.046- 1.845)	0.023
Townsend deprivation fifth rank		
1	1	
2	1.168 (0.784- 1.738)	0.444
3	1.321 (0.892- 1.956)	0.165
4	1.227 (0.813- 1.851)	0.331
5	1.227 (0.776- 1.941)	0.382
Study year		
1 year increase	1.073 (1.004- 1.147)	0.035

χ2 7, 6323=581.96, P<0.001, pseudo R2=0.26, α for dispersion 0.112 (95% C.I. 0.001-13.613)
RR rate ratio CI confidence interval

Mixed venous arterial leg ulceration incidence showed variation according to age, gender, and year of diagnosis. Increasing age, being female and increasing year of diagnosis were all associated with an increased risk of incident mixed venous arterial leg ulceration. Townsend fifth deprivation rank did not influence incidence density rates when examined either as a fifth, or when test for trend was analysed (p=0.304).

5.4.7 Results of initial assessment

From 2000 onwards, a total of 14,568 patients met the inclusion criteria as having an incident diagnosis of venous leg ulceration. Of these patients, 1608 (11.0%) had a database record of receiving a guideline recommended diagnostic assessment of their leg ulcer consisting of measurement of ABPI. Of those 479 patients diagnosed with an incident arterial leg ulcer during this period, 72 (15.0%) and 41/244 (16.8%) of patients diagnosed with mixed venous/arterial leg ulceration had a record indicating that their ABPI had been measured.

Next the temporal relationship between ABPI measurement and study year was examined for all three diagnoses of leg ulcers. These results are shown below in table 5.9.

Table 5.9 Proportion of leg ulcer patients with record of ABPI measurement, stratified by database leg ulcer diagnosis

	Venous leg ulcer n (%)	Arterial leg ulcer n (%)	Mixed venous arterial leg ulcer n (%)
2000	138/1687 (8.2)	6/50 (12.0)	5/19 (26.3)
2001	189/2013 (9.4)	2/54(3.7)	3/21 (14.3)
2002	223/2183 (10.2)	6/54 (11.1)	8/34 (23.5)
2003	247/2293 (10.8)	11/78 (14.1)	7/63 (11.1)
2004	253/2227 (10.9)	16/95 (16.8)	9/33 (27.2)
2005	285/2141 (13.3)	13/82 (15.9)	5/32 (16.2)
2006	273/2023 (13.5)	18/66 (27.2)	4/42 (9.5)

These results show that there has been an increase in the reported measurement of ABPI in patients of venous and arterial database diagnoses of leg ulceration. The results for mixed venous arterial leg ulcers did not show a clear relationship with study year. However the smaller numbers of patients with this diagnosis of leg ulceration means that small changes in either a positive or negative direction will have a large effect on the proportions observed. Next the frequencies and proportions of incident venous leg ulcer patients within each practice that had a record of receiving ABPI assessment were examined. The mean proportion of patients with a documented record of ABPI was 9% with values ranging from zero to 100% of all patients.

In the subgroup of patients with venous leg ulcers, further analyses of variables hypothesised to be associated with likelihood of ABPI measurement was undertaken using multilevel logistic regression. Only in this cohort were patient numbers per practice greater than five indicating that sample sizes were sufficient for multilevel methods to be used. Only cases for whom complete data were available were included in the analysis. Data from 13594/14,568 (93.3%) incident venous leg ulcer patients was included in the models. The only variable that had missing data was Townsend deprivation fifth rank. The results from this analysis are shown below in table 5.10.

Table 5.10 Results of multilevel logistic regression analysis of diagnostic assessment for patients diagnosed with venous leg ulceration.

	Model with patient variables only	**Model with patient and practice variables**
	Model 1	Model 2
Individual level variables	OR (95% CI)	OR (95% CI)
Age (years)	0.98 (0.97-0.99)	0.97 (0.96-0.98)
Gender Male Female	 1 0.84 (0.72-0.99)	 1 0.73 (0.54-0.99)
Deprivation fifth rank 1 (low deprivation) 2 3 4 5 (high deprivation)	 1 0.93 (0.74-1.18) 0.90 (0.71-1.14) 0.89 (0.69-1.14) 0.64 (0.47-0.87)	 1 0.89 (0.57-1.38) 0.82 (0.53-1.27) 0.81 (0.52-1.28) 0.44 (0.25-0.76)
Year of diagnosis	1.19 (1.13-1.27)	1.40 (1.28-1.53)
Practice level variables		
Mean practice list size		1.00 (1.00-1.00)
Intercept	-359.14	-683.95
Intra-class correlation co-efficient	50.3	49.2
Akiake's Information Criterion	8481.17	8445.65

The first model created included explanatory variables for patients only. This first model showed that the odds of receiving ABPI measurement were reduced if you were female (OR 0.84, 95% C.I. 0.72-0.99) and were resident in an area with a deprivation rank five compared to one (OR 0.64, 95% C.I. 0.47-0.87). Each increasing year of age was also shown to reduce your odds of receiving ABPI measurement (OR 0.95, 95% C.I. 0.97-0.99). Only one variable was shown to be positively associated with the odds of receiving ABPI measurement. Year of incident diagnosis was shown to be positively associated with increasing odds 1.19 (95% C.I. 1.47-1.77) of receiving ABPI assessment.

The second model included a potential explanatory variable related to the practice, the mean total list size of the practice. Mean practice list size did not show any significant association with the odds of receiving ABPI assessment. In this model the negative relationships between female gender and age intensified. The odds of females receiving ABPI assessment reduced to 0.73 (95% C.I. 0.54-0.99) and the odds associated with older age dropped to 0.97 (95% C.I. 0.96-0.98). The results of model selection using Akaike's information criterion suggested that model two, the model

containing patient and practice level data, was the best fit to the data as it had the smallest value. The results from this analysis suggest that despite an overall increase in the use of ABPI over the study period there are both gender and age related inequalities in the provision of ABPI assessment.

5.4.8 Results of the assessment of initial therapy

Treatments prescribed to all incident leg ulcer patients were examined and the results can be found in Appendix F. For consistency of comparisons between the earlier results of diagnosis, therapies prescribed during the time period January 2000 to December 2006 were examined. These therapies were grouped into the following categories; wound dressings, non-compression bandages, compression bandages, stockings and others. Others included magnet therapy, larvae, manuka honey, debridement (using an unspecified method), pentoxyfylline and vacuum assisted wound closure.

Between 2000 and 2006, 73.3% (10680/14568) of patients diagnosed with incident venous leg ulceration received a prescription for at least one form of wound therapy. 71.2% (341/479) patients with arterial leg ulceration received a prescription for at least one wound care therapy. For patients with mixed venous arterial leg ulceration, 86.5% (211/244) had a record of receiving a prescription for a wound therapy within. The most common treatments prescribed to all leg ulcer patients were bandages and dressings.

Further descriptive analysis was undertaken using the records of patients diagnosed with venous leg ulcers. In this group the relationship between prescription type and deprivation fifth of the patient. These results are shown below in table 5.11.

Table 5.11 Exploration of prescriptions issued to incident venous leg ulcer patients, stratified by deprivation fifth.

	1 (low deprivation)	2	3	4	5 (high deprivation)	Missing	Total
Compression	589 (20.2)	618 (20.7)	629 (21.2)	560 (18.8)	412 (13.8)	159 (5.3)	2,967
Bandages	854 (19.7)	887 (20.5)	920 (21.3)	810 (18.7)	606 (14.0)	248 (5.7)	4,325
Dressings	1946 (19.6)	2057 (20.7)	2072 (20.8)	1891 (19.0)	1340 (13.5)	647 (6.5)	9,953
Stockings	399 (20.8)	402 (21.0)	392 (20.5)	366 (19.1)	229 (12.0)	126 (6.6)	1,914
Other therapies	18 (23.1)	12 (15.4)	8 (10.3)	16 (20.5)	19 (24.3)	5 (6.4)	78
*Any therapy	2,106 (19.7)	2,174 (20.4)	2,228 (20.9)	2,022 (18.9)	1,452 (13.6)	698 (6.5)	10,680
None	696 (17.9)	697 (17.9)	832 (21.4)	774 (19.9)	613 (15.7)	276 (7.1)	3888
Total	2802 (19.2)	2871 (19.7)	3060 (21.0)	2796 (19.2)	2065 (14.2)	974 (6.7)	14,568

* Proportions of prescribed therapies will not add up 100 as patients may have been prescribed multiple therapies during the time period investigated.

The frequencies and proportions of all leg ulcer therapies prescribed to venous leg ulcer patients within the 30 days prior to or in the 90 days post incident diagnosis was examined and stratified by Townsend deprivation fifth rank. The results of this analysis shows that were no clear relationships between the frequencies of different products being prescribed to patients living in areas represented by different deprivation fifths. The only therapy prescribed that appeared to deviate widely from the expected frequency was the proportion of prescribed other therapies. Far greater numbers of patients living in areas with a deprivation rank of one and five received these therapies, whilst patients resident in areas with a deprivation rank of three were under represented. Due to the small proportion of all venous leg ulcer patients (0.5 %) receiving these other therapies, these results should be interpreted with caution as they may simply represent chance findings.

Next the frequency and proportion of patients receiving a prescription for compression therapy was investigated. 20.4% (2967/14,568) of venous leg ulcer patients were found to have received a prescription for compression, compared to 21.5% of arterial leg ulcer patients and 32.4% of all mixed venous arterial leg ulcer patients. Further descriptive analysis was undertaken to examine the temporal associations between the frequency and proportion of patients receiving prescriptions for compression therapy. These results are shown in table 5.12 below and are presented stratified by database diagnosis of leg ulceration.

Table 5.12 Proportion of leg ulcer patients prescribed compression therapy, stratified by database leg ulcer diagnosis

	Venous leg ulcer n (%)	Arterial leg ulcer n (%)	Mixed venous arterial leg ulcer n (%)
2000	355/1687 (21.0)	7/50 (14.0)	5/19 (26.3)
2001	394/2013 (19.5)	10/54(18.5)	5/21 (23.8)
2002	427/2183 (19.6)	11/54 (20.4)	4/34 (6.9)
2003	414/2293 (18.1)	19/78 (24.4)	15/63 (23.8)
2004	453/2227 (20.3)	19/95 (20.0)	12/33 (36.4)
2005	471/2141 (22.0)	18/82 (22.0)	19/32 (59.4)
2006	453/2023 (22.4)	19/66 (28.8)	19/42 (45.2)

The results of the analysis in table 5.12 above show that there has been an increase in the reporting of records for the prescription of compression bandaging therapy throughout the study period. This result was observed consistently for all three forms of leg ulcers investigated. The final descriptive analysis examined the proportion of venous leg ulcer patients that were prescribed or provided with compression bandaging within each practice. The mean proportion of patient's that received compression therapy was 20% although the range across all practices was zero to 100% of patients.

The results presented so far have relied upon descriptive analysis to explore associations between prescribing outcomes and a limited range of variables. Further exploration of the incident cohort of patients diagnosed with venous ulceration is undertaken next using multilevel analysis. This allows simultaneous adjustment of variables at the practice and patient level, that were hypothesised to influence prescribing behaviour and treatment allocation in general practice. This analysis sought to determine which factors were associated with receiving a report of a prescription for compression bandaging therapy within the 30 days prior to in the 90 days post diagnosis.

The first model examined patient level variables only and the second model expanded to include practice and patient level data. The results of these models and their corresponding model fit statistics are shown below in table 5.13.

Table 5.13 Results of multilevel logistic regression analysis of receiving compression bandages for patients with venous leg ulceration

	Model with patient variables only	Model with patient and practice variables
	Model 1	Model 2
Individual level variables	OR (95% CI)	OR (95% CI)
Age (years)	1.02 (1.01, 1.03)	1.02 (1.01, 1.03)
Gender Male Female	 1 1.13 (0.95-1.34)	 1 1.13 (0.95, 1.35)
Deprivation rank 1 (low deprivation) 2 3 4 5 (high deprivation)	 1 1.14 (0.88, 1.46) 1.12 (0.87, 1.45) 1.12 (0.86, 1.46) 1.12 (0.83, 1.50)	 1 1.13 (0.88, 1.46) 1.12 (0.87, 1.45) 1.12 (0.86, 1.46) 1.11 (0.83, 1.50)
Year of diagnosis	1.04 (0.99, 1.07)	1.04 (1.08, 1.09)
Practice level variable		
Mean practice list size		0.99 (0.99, 1.00)
Intercept (SE)	-83.87 (43.83)	-82.78 (44.41)
Intra-class correlation co-efficient (%)	44.7	44.6
Akiake's Information Criterion	12733.12	12734.51

The first model shown above in table 5.13, included patient level variables only. The results of this model demonstrated that the odds of receiving compression therapy increased by 2% (95% C.I 1.01-1.03) for each year older the patient was. The addition of practice list size in model two did not indicate a statistically significant relationship with the odds of receiving compression therapy, nor did it change the effect size of any variables included in the model. In neither model were the patients' gender, deprivation or the mean practice list size of the attending practice found to have a statistically significant relationship with the odds of receiving compression therapy. The results of model selection using Akaike's information criterion showed that model one was the best fit to the data as it had the lowest value. The results of this model demonstrate that only older patient age is positively associated with the odds of receiving a prescription for compression therapy.

5.4.9 Results of initial referrals

The analysis of referrals took place in three stages. First, incidents patients' records were searched for all referrals in the year following diagnosis. Descriptive analysis of frequencies and proportions of reports of referrals made to all providers is presented, stratified by database diagnosis of leg ulceration. Second, all patients' with incident venous leg ulcers records were searched for referrals deemed to be related to their leg ulceration.

The full results of all referrals, general and leg ulcer related is shown in appendix G. These results from this analysis suggest that far greater numbers of patients diagnosed with arterial and mixed venous arterial leg ulcers were referred on for further treatment by any specialist provider. Referral rates for patients' with these two forms of leg ulceration were in excess of 69%, compared to less than 30% of persons with venous leg ulceration.

Wide variation in leg ulcer related referral rates were also observed amongst patients with different forms of leg ulcers. Once again, referral rates were substantially higher in patients diagnosed with arterial and mixed venous arterial compared with venous leg ulcers. The referral rate of patients referred for further leg ulcer treatment was 48% for arterial leg ulcer patients, 39.7% for mixed venous arterial leg ulcer patients and 16.1% for those with venous leg ulcers. The final descriptive analysis involved looking at the proportion of incident venous leg ulcer patients within each practice that received a record of a leg ulcer specific referral. Mean values were 10.6% with values ranging from zero to 75% of patients within different practices.

The third and final stage of analysis consisted of the development of multilevel models. In the cohort of patients diagnosed with venous leg ulceration, sufficient patient numbers were available to undertake these analyses. Data from these complete cases were then used to fit multilevel models exploring the effect of explanatory variables on the odds of receiving referral for further leg ulcer management. These data were also used to examine the relationship referrals to all providers. The results of these analyses are firstly shown below in table 5.14 for the model examining the relationship between explanatory variables and leg ulcer specific referrals.

Table 5.14 Results of multilevel logistic regression analysis of leg ulcer referral for patients with venous leg ulceration

	Model with patient variables only	Model with patient and practice variables
	Model 1	Model 2
Individual level variables	OR (95% CI)	OR (95% CI)
Age median centred	0.98 (0.98, 0.99)	0.98 (0.98, 0.99)
Gender Male Female	 1 0.97 (0.83, 1.14)	 1 0.97 (0.84, 1.14)
Deprivation rank 1 (low deprivation) 2 3 4 5 (high deprivation)	 1 1.01 (0.81, 1.26) 0.93 (0.74, 1.16) 0.82 (0.65, 1.04) 0.89 (0.68, 1.15)	 1 1.00 (0.80, 1.26) 0.92 (0.73, 1.16) 0.82 (0.65, 1.04) 0.88 (0.68, 1.14)
Year of diagnosis	1.15 (1.09, 1.20)	1.49 (1.36, 1.63)
Practice level variables		
Mean practice list size		0.99 (0.99, 0.99)
Intercept (SE)	-274.54	-270.94
Intra-class correlation Co-efficient (%)	38.3	37.8
Akaikes Information Criterion	7695.09	7692.48

First, model one was created to explore the effect of patient level variables on the odds of receiving a referral for further ulcer care. Only year of diagnosis (OR 1.49; 95% CI 1.35-1.64), showing that rates of referral were increasing over time and age (OR 0.98; 95% C.I. 0.98-0.99) showing a small but significant relationship between increasing age and having a record of a referral to a leg ulcer specific care provider. No other patient level variables were found to be associated with the odds of a leg ulcer specific referral.

Second, model two was created including variables at both the patient and practice level. This model showed that only three explanatory variables included in the model contributed to the variation in odds of referral. These explanatory variables were younger age, year of diagnosis and mean practice list size. Specifically, the model showed that the odds of being having a database record of referral to providers for leg ulcer care increased throughout the study period and was lower in patients that attended smaller practices. Odds of referral increased by 1.49 (95% C.I. 1.36-1.63) as year of diagnosis increased, decreased by 0.99 (95% C.I. 0.98-0.99) as mean practice list size and decreased as patient age increased OR 0.98 (95% C.I. 0.98-0.99). The results of model selection using Akaike's information criterion suggested that this last model was the best fit to the data. The results from this analysis indicate that there is a slight reduction in the odds of being given a leg

ulcer specific practice in smaller practices, although there is a much larger increase in the odds of all patients receiving a leg ulcer specific referral throughout the study period investigated.

Finally, the relationship between explanatory variables and the odds of receiving any referral was investigated. The results of this analysis is shown below in table 5.15.

Table 5.15 Results of multilevel logistic regression analysis of all referrals for patients with venous leg ulceration

	Model with patient variables only	**Model with patient and practice variables**
	Model 1	Model 2
Individual level variables	OR (95% CI)	OR (95% CI)
Age median centred	1.00 (0.99-1.01)	1.00 (0.99-1.01)
Gender Male Female	 1 0.99 (0.88-1.11)	 1 0.99 (0.90-1.01)
Deprivation rank 1 (low deprivation) 2 3 4 5 (high deprivation)	 1 1.05 (0.88-1.24) 0.92 (0.78-1.10) 0.99 (0.84-1.19) 1.05 (0.86-1.28)	 1 1.04 (0.90-1.20) 0.94 (0.81-1.09) 0.99 (0.86-1.16) 1.04 (0.87-1.23)
Year of diagnosis	1.32 (1.15-1.50)	1.27 (1.19-1.35)
Practice level variables		
Mean practice list size		0.99 (0.99-1.00)
Intercept (SE)	-549.61 (137.07)	-477.11 (66.15)
Intra-class correlation Co-efficient (%)	46.4	52.6
Akaikes Information Criterion	15720.37	15720.65

The results of the final analysis indicated that only increasing study year had a statistically significant relationship with the odds of receiving a referral to any care provider in the year following incident diagnosis. This same finding was observed in both the evaluation of patient level and the combined patient and practice level variables showing that odds of referral were increasing by 32% (95% C.I. 1.15-1.50) per year over the study period. The result of model selection using Akiake's criteria suggested that model one, the model with patient level variables only, was the best fit to the data.

5.5 Discussion

5.5.1 Statement of principal findings

The THIN database was interrogated to identify patients who had a database record of an incident leg ulcer recorded prospectively during the study period of 2000 to 2006 and prevalent leg ulcers between 2001 and 2006. The socio-economic measure available in this database was the Townsend deprivation score fifth. Areas were ranked between one and five, with one representing the least and five representing the most deprived areas.

The first aim of the study was to determine if socio-economic factors were associated with the distribution of leg ulceration. Over 15,000 patients met the eligibility criteria of having either incident or prevalent leg ulceration of any database diagnosis. Over 90% of leg ulcer patients identified had a database diagnosis of venous leg ulceration. The remainder of patients had a database diagnosis of either arterial or mixed venous arterial leg ulceration.

For patients with a database record of incident or prevalent venous leg ulcers, results of regression demonstrated a 10% increase in risk with higher deprivation rank. This social gradient in risk was observed whilst controlling for other risk factors in the analysis such as age, gender and year of study. Other variables shown associated with higher rates of venous incidence and prevalence were older age and female gender. For persons with arterial leg ulceration, regression analyses showed this same 10% increase in risk with increasing deprivation. These higher rate ratios were only shown be significant in persons living in an areas with a Townsend deprivation rank of four or five. Neither incidence nor prevalence of mixed arterial venous leg ulcers were shown to have a statistically significant relationship with deprivation. In both cases prevalence rate ratios were shown to increase over the study period. Gender was only shown to have a statistically significant effect upon mixed venous arterial leg ulceration, with female gender shown to be associated with increased prevalence and incidence rate ratios. Gender was not shown to have any relationship to arterial leg ulceration. For all three diagnoses of leg ulceration examined, regression analysis also showed that incidence and prevalence rate ratios were increasing over time. These increases varied between 10 and 18%.

The second aim of this study was to examine if socio-economic differences between patients contributed to variations in the initial diagnosis and management of patients' leg ulceration. First, the diagnostic methods used were evaluated. Guidelines produced in the UK all recommend that leg ulcer patients have their ABPI measured to guide appropriate management (CREST 1998; SIGN 1998; RCN 2006). Diagnostic assessment of leg ulcers, consisting of the reported measurement of patients' ABPI, was infrequently performed irrespective of the type of leg ulceration examined. Over the study period, reported rates of diagnostic assessment ranged from

9.9% in patients with venous ulceration to 15.4% in patients with mixed venous arterial leg ulceration.

The cohort of patients diagnosed with venous leg ulceration was large enough to examine the relationship between deprivation and reported ABPI assessment, whilst taking into account the nested structure of the data, patients nested within practices. Multilevel logistic regression analyses showed that patients living in areas of high material deprivation, rank five, were less likely to have received a report of a diagnostic assessment consisting of ABPI measurement. Despite this, the results indicated that the odds of receiving ABPI were improving over time. This increase was not equally distributed amongst the populations with the greatest risk of developing leg ulceration. The population most likely to develop leg ulcers were those patients living in areas of high deprivation and older women who were also the least likely to receive guideline recommended diagnostic assessment. This may indeed lead to greater health inequalities if the population most likely to develop leg ulcers is the least likely to be adequately diagnosed.

Second, initial treatments prescribed in the first three months post diagnosis and were examined to determine if there were socio-economic differences. Irrespective of the database diagnosis of leg ulceration given, a wide range of therapies were prescribed to patients. With the exception of compression therapy for venous leg ulceration (O'Meara et al. 2010) treatments for leg ulceration of other forms are currently not well served by evidence of effectiveness. Stratified analysis did not indicate any large differences in therapeutic class of prescribing associated with Townsend deprivation rank of leg ulcer patients in any diagnostic category. The majority of patients received bandages and dressings.

The odds of receiving compression therapy were examined using multilevel logistic models in the subgroup of patients diagnosed with venous leg ulceration. Townsend deprivation rank was not shown to have a statistically significant relationship with venous leg ulcer patients' odds of receiving compression therapy as a first line therapy. However, increasing patient age and increasing year of diagnosis were both shown to be associated with higher odds of receiving compression therapy.

The third and final aim of the study was to examine if there were variations in the nature of referrals by socio-economic factors. First, all referrals were examined descriptively. More patients with arterial and mixed leg ulcers were referred than those diagnosed with venous leg ulcers. Second, leg ulcer specific referrals were examined. Once again more patients with arterial and mixed leg ulcers were referred than those diagnosed with venous leg ulcers.

In the sub-group of patients diagnosed with venous leg ulcers, patient numbers were sufficient to explore the relationship of socio-economic factors and referrals using multilevel logistic regression. These analyses showed that the only factors associated with the odds of referral were year of diagnosis and mean practice list size. Increasing year being associated with higher odds of referral and mean practice list size, with patients attending smaller practices having lower odds of receiving a leg ulcer related referral. Referral decisions for the treatment of venous leg ulceration were not shown to be statistically associated age, gender or socio-economic position. Examination of all referrals showed that only increasing study year was associated with increases in the odds of referral

5.5.2 Strengths and weakness of the current study

The work of this chapters study has a number of weaknesses. First, none of the codes used to identify leg ulcer patients in the THIN database were validated in this study. This is in contrast to the previous chapters study using the GPRD. Despite this limitation it is noted that over half of the practices that contribute to the THIN database also contribute to the GPRD (The Health Improvement Network 2007). In practice this should mean that at least half of the contributing data has been previously validated for the coding of venous leg ulceration.

The major weakness of the current study and one that is common to all studies using deprivation indicators from primary care is the temporal nature of deprivation indicators. This study used the Townsend deprivation rank of the area that was assigned to the residence that the patient was living in as of 2006. However, these Townsend deprivation fifths are based on data from the 2001 census. These same criteria were also applied by the database administrators when assigning fifths to the denominator populations that were used to calculate both incidence and prevalence of leg ulceration. The possibility of reverse causation in the current study must be considered. The possibility that the development of a leg ulcer caused a change in residence to a more deprived area cannot be excluded. Despite this there was only limited evidence of moves over the study period in the group of patients with leg ulcers with less than 100 patients having multiple ranks. This suggests that multiple moves were not that common in our patient group during the study period. The majority of patients observed in this study were aged in excess of 65 years and rates of internal migration within the UK are lower in this age group (Hussain &Stillwell 2008).

Finally the possibility of the results being subject to ecological fallacy cannot be excluded. The ecological fallacy warns against assuming that all those living in deprived areas are themselves necessarily deprived (Fieldhouse &Tye 1994; Sloggett &Joshi 1998). The results of this study therefore make no inferences about the socio-economic position of the leg ulcer patients' themselves. The inferences observed in this study therefore refer only to association with the area

in which an individual lives being associated with the burden of disease and management decisions observed.

A key strength of the study is the sample size and the data source used to undertake the study. It the largest study yet undertaken to evaluate the effect of individual level socio-economic deprivation on both the burden and management of leg ulceration. Methods have been used that allow the quantification of the effects of multiple variables, on both the burden and management of the conditions. The results obtained were not subject to any recall or non-responder bias that may have been present if primary care professionals had been surveyed about their practice. Furthermore, the study was adequately powered to examine the outcomes identified and contained data contributed from the entire UK, and is likely representative of current national practice.

5.5.3 Strengths and weakness of the current study in relation to existing literature

The incidence and prevalence rates obtained in this study are broadly comparable with previous studies. Crude prevalence rates of 0.08-0.12 per 100 persons for women and 0.05 to 0.08 per 100 persons for men are within the bounds of the results found in the systematic review by Graham et al. (2003a). Rates of incidence are lower than those reported by Margolis et al. (2002). This is to be expected given that the current studies results came from a general adult rather than an elderly population. These are, however, comparisons of unstandardised rates and must be interpreted cautiously.

There is some suggestion that migration patterns may bias some of the results observed in this study as work undertaken by Norman et al. (2005) indicated that people in poorer health were more likely to migrate to more deprived areas thus contributing to more ill health in the area that they move to. However, work by Brown & Leyland (2009) suggests that the relationship between age and deprivation may be more complex when factors such as population stability and turnover are accounted for. In their recent study in Scotland, they found that populations in deprived areas where populations were decreasing had higher rates of reported limited long term illness relative to deprived areas with more stable populations (Brown &Leyland 2009). The median age of the population developing leg ulcers are of retirement age if not older, and older people are less likely than younger people to move (Bailey &Livingstone 2007). Given, therefore that majority of patients develop leg ulcers later in life it is felt that this is unlikely to introduce considerable bias into the results observed.

The work conducted in this chapter adds further weight to the accumulating evidence showing social differences in prevalent leg ulcer rates (Fowkes &Callam 1994; Moffatt et al. 2006). The results obtained in the current chapters study could not confirm earlier results by Callam et al.

(1988) which stated that persons with lower occupational social class had ulcers of longer duration. Duration data from the THIN database was subject to the same problems as duration data obtained in the study conducted in chapter four using the GPRD. The results of this study expands upon earlier findings by Fowkes & Callam (1994) and Moffatt et al. (2006) by demonstrating that incidence as well as prevalence is also influenced by deprivation. Furthermore, these findings show that these associations may be stronger in patients with venous and arterial leg ulcers.

No other studies have yet examined the influence of socio-economic factors on the management of any aspect of leg ulceration. Studies that have examined the management of leg ulceration within primary care have found similarly low levels in the reported use of Doppler ultrasound assessment. Hickie et al. (1998) found that only 8% of all professionals in primary care reported using Doppler ultrasound. Studies have also shown that many practitioners working with leg ulcer patients do not have confidence in their ability to conduct ABPI assessment using Doppler ultrasound (Hickie et al. 1998; Schofield et al. 2000).

Other studies examining usage rates of compression have reported higher rates ranging from 50 to 90% of all patients (Hickie et al. 1998; Lorimer et al. 2003b; Vowden &Vowden 2009) compared to this study's results which ranged from ~20 to 30%. With the exception of one study which reviewed the case notes of 66 patients (Lorimer et al. 2003a), other results were based on surveys of health professionals with poor response rates (Hickie et al. 1998). The reported usage rates from these studies may paint an overoptimistic picture of the realities of clinical practice. It remains unclear whether these lower usage rates of compression therapy observed in the present are a reflection of referral practice meaning that treatment decisions are not being made until patients are referred to other practitioners.

Studies of the management of other diseases have shown that differences in management due to the age and sex of patients can occur. A recent study found differences in prescriptions and hospitalisations between men and women for a range of conditions including diabetes, asthma and coronary artery disease (Stock et al. 2008). These findings were observed even when the results had been controlled for the age and co-morbidities of the patients (Stock et al. 2008).

It has been shown that when compression has been prescribed, patient compliance is not always achieved (Van Hecke et al. 2008). Edwards (2003) examined reasons for non-compliance with compression therapy and highlighted issues related to pain and discomfort of bandaging and poor explanation to patients' of the role of compression therapy for the treatment of leg ulceration.

There have been no other published studies which have reported referral rates for leg ulcer services from general practices so no comparison with other results can be undertaken. Therefore the current study fills a much needed gap in our understanding of referral practices for leg ulcer services from general practice.

Ideally, this study would have statistically evaluated the impact of other known risk factors (such as smoking and obesity) in the development and prognosis of leg ulceration. However, concern about the coding of smoking data in primary care databases has been raised. Previous work undertaken by Lewis & Brensinger (2004) has shown that when the coding of smoking status in the GPRD was compared to rates from a survey of the same population database rates were lower than expected. There is no evidence to suggest that the THIN database would not have similar limitations. Other risk factors such as body mass index are also not routinely recorded in general practice databases. Furthermore the introduction of the Quality and Outcomes framework is likely to have changed reporting practices of smoking and other lifestyle data as incentives now exist for practitioners to report data. In order not to introduce potential bias into the analysis these behavioural risk factors were not included in explanatory models, but do warrant research in future research where they have been prospectively collected for all participants.

No validation of was undertaken of the data used in this study. However, this study used codes to identify venous ulcer patients that were previously validated using the GPRD (Margolis et al. 2002). It should further be remembered that at least half of the practices contributing data to the THIN database also contribute to the GPRD (The Health Improvement Network 2007). Epidemiological validation studies have been undertaken using the THIN database (Lewis et al. 2007) comparing data from practices that contribute to the GPRD and those that only contribute to THIN. This study by Lewis et al. (2007) found that data contributed to the GPRD appeared as valid as that contributed to the THIN database alone. Therefore there is unlikely to be bias introduced when using the case identification strategy for venous leg ulceration. The validity of other diagnoses of leg ulceration does however remain unknown.

It must also be emphasised that the results obtained in this chapter are based on the data recorded in the database. There may have been valid clinical reasons why some subgroups of patients were not given ABPI assessments or compression therapy, however there is no way to record this using Read codes and it was not possible to directly access patient notes for further information. In patients with a range of conditions including diabetes, readings from ABPI may not be accurate (RCN 2006). This may mean that practitioners may be reluctant to use this method of diagnostic assessment in some leg ulcer patients. In the current study the results suggested that older patients were most likely to have a report of a prescription for compression therapy. Although it cannot be

evaluated using data from the THIN database it is hypothesised that younger patients in particular may have strong negative views of wearing compression due to negative opinions of the aesthetics and comfort. Finally, there may be other valid reasons why a proportion of patients do not have a record of a prescription issued within the first three months of diagnosis. For example, a contraindication to compression therapy. There is no provision of Read codes in the database that would facilitate the recording of this information.

Although there are no reasons to suggest that accuracy is an issue with the data, this cannot be ruled out as validation was not undertaken. There is also no way to verify what the proportion of self-referral to specialist services may be. In some areas of the UK patients are able to self-refer to leg ulcer services, such as community nursing, meaning that there would be no record of referral in patients' database record.

5.5.4 Meaning of the study

Socio-economic position was shown to influence both the development and management of leg ulceration. This effect was shown to operate independently and in addition to other known risk factors for leg ulcers such as age and gender. Deprivation was also shown to be related to differences in the initial diagnosis of venous leg ulcer patients although not observed to be related to management.

6.0 Does deprivation influence healing and other leg ulcer patient outcomes?

6.1 Introduction

The previous chapters (four and five) have built up a picture of the socio-demographic profile of patients seeking treatment for leg ulceration within UK general practice, as well as describing the relationship between socio-economic factors and the management of leg ulcers. Primary care data collection is heavily focussed on both the diagnosis and treatment of patients and, in the case of leg ulceration, does not often contain information regarding relevant outcomes such as healing. This is unlikely to be a situation that is unique to the clinical management of leg ulceration. For many chronic conditions, patients are unlikely to notify or visit their health care practitioner if their condition improves. This means that there is no opportunity for this information to be routinely collected or recorded.

To obtain outcome data following treatment for leg ulceration, other sources of data were required. In the Department of Health Sciences at the University of York, where I am based, there have been two recent randomised controlled trials (RCTs) that have evaluated the effectiveness of different interventions for the treatment of leg ulcers.

RCTs are arguably the most effective way of producing evidence to establish the effectiveness of interventions for clinical care and the results can be further enhanced by inclusion in systematic reviews, the results of which may significantly influence policy and practice.

Previous research provides some evidence of associations between deprivation and healing as well as deprivation and adverse events. Earlier work conducted by Callam et al. (1988) and Franks et al. (1995b) suggest that measures of socio-economic position may be related to leg ulcer healing. The study by Callam et al. (1988) found that persons of lower socio-economic position had longer duration of leg ulceration with over 70% of social class 4 and 5 patients having ulcers of five of more years duration. Franks et al. (1995b) found that lack of central heating, which may be a marker of material deprivation, was positively associated with a venous leg ulcer not healing within 12 weeks of the application of a standardised treatment. Furthermore, a study investigating post operative coronary artery bypass surgical rates of MRSA found a socio-economic gradient in their development (Bagger et al. 2004). Based on the results of these studies, it is hypothesised that there may be associations between socio-economic factors and the outcomes of healing and adverse events of leg ulcer patients. Utilising data from clinical trials of therapies for leg ulcer patients provides an ideal setting in which to test this hypothesis.

There is a further body of research that has shown that there strong negative associations between perceptions of stress and wound healing. With one exception (Cole-King &Harding 2001) , the results of these studies came from investigations undertaken in healthy populations with experimentally induced acute wounds (Walburn et al. 2009). Normal wound healing follows a cascading process of haemostasis, inflammation, proliferation and tissue remodelling which leads to at least a partial wound reconstruction and healing (Werner &Grose 2003). The healing process of chronic wound differs from that of acute wounds with chronic wounds being less likely to heal and more likely to recur. In contrast to acute wounds, chronic wounds are likely to have a lengthier process of inflammation, high levels of proteases and low levels of growth factors (Kane 2007).

Explanations for the links between perceptions of stress and socio-economic position relate to two separate interlinking theories. First, low socio-economic position has been shown to be related to increased exposures to stressors in the environment and people with low socio-economic position also have fewer psychosocial resources to respond to these stressors, compared to higher socio-economic position counterparts (Kristenson et al. 2004). Second, exposure to chronic stressors may initiate adverse behavioural responses as coping mechanisms, such as smoking or increased alcohol consumption, which synergistically work to exacerbate the negative physiological effect of stress (Stringhini et al. 2010). These two pathways provide a useful theoretical framework to explain the potential ways in which socio-economic position may be related to both adverse exposures and adverse outcomes such as impaired wound healing.

How might SEP impact on trial outcomes

There is some debate as to the definition of an ideal clinical trial population as well as the preferred methodological approach to conducting randomised controlled trials. Schwarz and Lellouch (1967) were the first to argue that there are two philosophical approaches to the conduct of a randomised controlled trial; the explanatory and the pragmatic approaches.

The methodology behind the explanatory approach to the conduct of clinical trials seeks to evaluate precisely defined interventions in a highly selected patient group under optimal conditions (Treweek &Zwarenstein 2009). The pragmatic approach, in contrast is to employ a broader trial entry criteria which may mean that participants have more co-morbid conditions, demonstrate varying levels of compliance and use other medications (Godwin et al. 2003). The different methods employed to conduct randomised controlled trials will have a different impact on the external generalisability of the findings. To their broader trial entry criteria findings of pragmatic trials will apply to wider proportions of the population than those of explanatory trials, where the entry criteria for trials are limited to a select patient group.

Irrespective of whether a pragmatic or explanatory approach is employed, there are significant threats to the external validity or generalisability of clinical trials if there have been systematic exclusions of participants, who will be candidates to receive the treatment post-trial. One example of the systematic exclusion of a population from clinical trials is that of women. Systematic exclusion of women from clinical research has been noted in a wide spectrum of research, including laboratory animal studies through to randomised controlled trials in humans. These exclusions have even been found in the investigation of diseases that disproportionally affect females (Check Hayden 2010). The implications of these exclusions have not only meant that efficacy data from these trials may not be relevant for women, the results may further lead to incorrect dosage recommendations for women that may have deleterious health impacts (Holdcroft 2007).

Any lack of external generalisability may be further compounded when the results of many trials are pooled in a meta-analysis. A recent systematic review of systematic reviews evaluating interventions for smoking cessation and interventions for the treatment of HIV found that only 60% of the systematic reviews included reported baseline characteristics, and even in these studies important information pertaining to the age, sex, ethnicity and socio-economic position of patients was frequently missing (Ahmad et al. 2010).

Despite extensive searching no clinical trials in the area of leg ulceration, or wound care more widely, were found to have reported the details of any socio-economic position indicators of patient populations. Consequently the socio-economic or demographic representativeness of patients included in clinical trials of leg ulceration remains unknown.

Although the two RCTs of treatments for leg ulceration undertaken by researchers at the University of York did not examine patient socio-economic position as a potential confounder or modifier of treatment effects, they did collect the residential postcode of all trial participants. Utilising the residential postcode, a Townsend deprivation score can be given to each trial participant. First, this allows an exploration of the relationship between socio-economic position and leg ulcer healing and adverse events. Second, this enables further examination of the representativeness of the socio-economic position of trial participants, making comparison with the THIN database described in chapter five.

6.1.1 Background to VenUS I and II

The two recently conducted leg ulcer therapy trials conducted at the University of York are known as VenUS I and VenUS II. The acronym VenUS refers to venous ulcer study.

VenUS I was undertaken to compare the effectiveness of two different types of bandages (four layer compression bandages *vs* short stretch bandages) for the treatment of venous leg ulceration (Iglesias et al. 2004). VenUS I recruited a total of 387 patients in England and Scotland between April 1999 and December 2000. The main outcome for this trial was the time to complete healing, all patients were followed for until they healed or for a maximum of 30 months.

VenUS II evaluated the effectiveness of larvae (delivered in either bagged or loose form) compared with hydrogel, to heal sloughy venous or mixed venous arterial leg ulcers (Dumville et al. 2009). Secondary outcomes included quality of life, use of resources, adverse events and the effect on the microbiology of wounds. This trial recruited 267 patients between July 2004 and May 2007 from England and Northern Ireland.

In both VenUS I and II, time to complete ulcer healing was the primary outcome of interest.

6.1.2 Rationale for the current study

Only one study was found that evaluated the role of socio-economic position as a potential effect modifier in the leg ulcer healing process (Franks et al. 1995b) and none were found that examined relationships with adverse events or socio-economic representativeness of leg ulcer trial populations. As socio-economic differences in both the development and management of leg ulcers have been demonstrated in chapter five, it is important to determine what effect these differences may have on leg ulcer outcomes. Knowledge of any differences can be used to ensure that future management strategies are appropriately targeted to populations with the greatest needs.

The representativeness of trial samples could not be assessed up to now as large non age-restricted population-based incidence and prevalence studies had not been conducted prior to commencement of these clinical trials. The epidemiological studies, undertaken in chapters four and five, provide a relevant contemporary evidence base of the demographic and socio-economic characteristics of the ambulatory population of people with leg ulcers. This work also allows for the relationship of socio-economic factors with leg ulcer healing and adverse events to be quantified. Finally, it also allows comparisons between trial populations and the primary care treated leg ulcer population to be undertaken and the representativeness of trial populations assessed.

6.2 Research questions

There are several questions that will be answered in this chapter. These questions are;

1. Is low socio-economic position negatively associated with leg ulcer healing?
2. Is low socio-economic position negatively associated with infection or other treatment or non treatment related adverse events?
3. How representative of the age, gender and socio-economic profiles of registered general practice patients in the GPRD and THIN databases are trial patient's participants?

6.3 Methods

In this chapter, the main analyses and the exploration of adverse events in both VenUS I and II will be replicated with socio-economic variables added to the analyses to determine what impact, if any, these variables have on the clinical trial outcomes of healing and adverse events. The full details of the previously conducted analyses, and the methods used can be found in the full trials reports published by Iglesias et al.(2004) and Dumville et al.(2009). The methods used to complete the primary analyses of both VenUS I and II are summarised in brief below and the additional methods used in this chapter are then described.

6.3.1 Summary of methods for the VenUS I analysis

VenUS I was conducted to compare the effectiveness of two forms of compression bandaging for the healing of venous leg ulcers. The two types of compression bandaging evaluated in the trial were the four layer bandage (4LB) (a multilayer, elastic compression bandage) and short stretch bandages (SSB) (a multilayer inelastic form of compression bandage). The primary outcome was the complete healing of patients' leg ulcers. To be eligible for inclusion in the study, patients needed to be 18 years or over and have a venous leg ulcer of at least one week's duration; with a dimension of at least 1cm in length or width, and that had not previously failed to heal using one of the two trial bandages. In addition, patients needed to have an ankle brachial pressure index of at least 0.8, and not have diabetes.

Patients were recruited from nine different UK sites representing a range of urban and rural sites where care was delivered by a number of different services including domiciliary visits, nurse led clinics and tertiary referral clinics. As reported by Iglesias et al. (2004) randomisation was stratified by prognostic variables. These were ulcer duration, episode, area and treatment centre. Leg ulcer area and duration were chosen as they are known prognostic markers of leg ulcer healing. It has been established that larger and older ulcers are less likely to heal compared to smaller and newer

leg ulcers (Margolis et al. 2004a). In VenUS I leg ulcer duration was classified as <6 months duration or >6 months duration, whilst ulcer size was classified as being >10 or ≤10cm^2. Centre was also chosen as a stratifying variable. Finally leg ulcer episode was chosen as a stratifying variable as either the first or subsequent leg ulcer episode. Baseline demographic information collected from all patients included age, gender, height, weight, ulcer location, ulcer duration, number of episodes of leg ulceration, ankle mobility, ankle circumference, ulcer position and patient mobility.

The statistical analysis conducted in this chapter is undertaken in two phases. First, the bivariate relationship between variables included in VenUS I analyses and the primary outcome of healing is evaluated. This involves examining each variable in a Cox proportional hazards model and estimating a hazard ratio value to determine if the variable had a positive, negative or null relationship to healing. Variables examined include treatment arm (4LB *vs* SSB), ulcer duration, ulcer area, ulcer episodes, patients' weight, ankle mobility, Townsend deprivation fifth and Townsend deprivation score.

Second, Cox proportional hazard models are estimated to examine differences in rates of healing between patients randomised to treatment with four layer bandage compared to those treated with short stretch bandage and socio-economic position is included in the models. Two models are created, the first examined the relationship of fifths of Townsend Deprivation Index and the second included the Townsend Deprivation Index as a continuous score. The two Cox proportional hazard models are adjusted for variables shown to be related to leg ulcer healing.

The relationship between Townsend deprivation rank and adverse events is investigated by comparing both the type and overall frequency of adverse events encountered participants living in each deprivation fifth. Where data is available, examination of the relationship between Townsend deprivation fifth and infection rates is also performed.

6.3.2 Summary of methods for the VenUS II analysis

VenUS II was conducted to compare the effectiveness of larval therapy to hydrogel in healing sloughy venous and mixed venous arterial leg ulcers. In this trial larval therapy was delivered in two forms, loose and bagged. The primary outcome of this trial was time to complete healing of the reference ulcer. There were two phases to the treatment that patients received in this trial. Phase one consisted of a debridement phase where participants were treated with either larval therapy or hydrogel until they healed or they had completed at least six months in the trial without debridement occurring, or the decision was made to cease trial treatment. Phase two then consisted of all patients receiving either high or reduced compression therapy as appropriate to their ABPI measurement or tolerance of the therapy.

Patients were eligible for inclusion in the trial if they had sloughy or necrotic leg ulcers (with at least 25% cover), had their ulcer for at least one week, the ulcer was at least 5cm^2 in diameter or less than 5cm^2 but not healing (defined as no change in wound in the previous month), were 18 years or over, had an ABPI measurement of at least 0.6 and were receiving their care from community nurse domiciliary visits or from leg ulcer clinics held in hospital or a community setting. Patients with diabetes mellitus were eligible for inclusion if their blood sugar was well controlled (defined as HbAc1c equal to or less than 10%). Patients with rheumatoid arthritis were also eligible if their leg ulcers were deemed to be venous in origin.

The original primary analysis consisted of a log rank test followed by a Cox proportional hazards model. The current analysis replicates these two original analyses, as well as performing bivariate analysis of the relationships between variables included in the full regression model and the primary outcome of healing. In keeping with the original Cox proportional hazards model, this analysis included the same stratification and prognostic variables. The stratifying variables included in the current analysis are centre and baseline ulcer area (≤5cm^2 *vs* >5cm^2). The prognostic variables included in the analysis are ulcer duration, ulcer type and ankle brachial pressure index measurement. In the original analysis plan it was decided *a priori* that if no significant differences were found between the loose and bagged larvae group then results of the proportional hazards model would be presented for the larval therapy group as a whole. The results of the original analysis showed this to be the case and so this approach is replicated in the current analysis. In this current analysis an indicator of patients' socio-economic position, the Townsend deprivation fifth is added to the variables included in the original Cox proportional hazard model examined both as a score and a fifth rank.

The adverse events recorded in VenUS II are further examined in this current analysis. First, the previously published results of adverse events are stratified by Townsend deprivation fifth to explore potential relationships. Second, the negative binomial regression originally undertaken to examine the relationship between numbers of adverse events in each arm of the VenUS II is replicated as per the original analyses only in this current analysis the Townsend deprivation fifth is added to the model. As per the original analysis adjustment is made for ulcer size, duration and ulcer type.

6.3.3 Deprivation measure

The indicators of socio-economic position used in these analyses are the Townsend deprivation score and the Townsend deprivation fifth. To ensure that the data collected is comparable with the Townsend deprivation fifths calculated by the THIN database administrators (used in chapter 5)

fifths for the Townsend scores are calculated nationally at the geographical unit of Output Area of the 2001 census. Output areas are used by the Office for National Statistics to classify geographical areas with common characteristics, consisting of populations of approximately 125 households (Office for National Statistics 2010b). The variables required to calculate the Townsend deprivation score are obtained from 2001 census data and are shown below in table 6.1. The values for overcrowding and unemployment were transformed using the natural log function. Each component score of the Townsend deprivation index is z standardised by applying the mean and standard deviation percentages for all of the output areas. Townsend scores are then created by adding together all the z standardised components, and fifths produced by dividing all scores into five even groups for all areas nationally.

Table 6.1 Variables used from the 2001 census to calculate the Townsend Deprivation Index

Component	Variables*
Unemployment Unemployed residents over 16 years as a proportion of all economically active residents aged over 16.	Unemployed residents aged 16 years and over ks09a0005/ Economically active residents aged 16 years and over ks09a0002+ ks09a0003+ ks09a0004+ ks09a0005+ ks09a0006 *100
Overcrowding Households with 1 and over persons per room as a proportion of all households	Households with more than one person per room ks0190004 /All households ks0190001 *100
Non car ownership Households with no car as a proportion of all households	Households with no car ks0170002/ all households ks0170001
Non home ownership Households not owning their home as a proportion of all households	Households not owning their home 100- owns outright ks0180002+ owns with a mortgage or loan ks0180003/ all households ks0180001

* The variables shown are those used to calculate the Townsend score for England. Equivalent codes exist for the calculation of Townsend scores in Wales, Northern Ireland and Scotland and can be provided upon request.

Patients' postcodes were collected as part of the baseline data for both VenUS I and II. Each patient's postcode is then linked to the output area corresponding to the geography of the postcode, to which a Townsend deprivation score from the national values is linked.

6.3.4 Methods for the analysis of trial sample representativeness

Descriptive analyses is performed to compare the participant demographic characteristics of the two VenUS trials to the leg ulcer populations seeking care from general practices contributing data to the GPRD and THIN databases. Due to the large sample size of leg ulcer patients identified in the primary care databases the decision was made not to undertake any tests of statistical significance. This is because small differences between the groups, which may not be clinically significant, will result in statistically significant differences.

Patient demographic variables include age, gender and Townsend deprivation fifth membership. Mean values and their corresponding confidence intervals are calculated as well as medians and ranges. Frequencies and proportions of categorical variables, such as gender and Townsend deprivation fifth are reported.

6.3.5 Statistical analyses

All statistical analyses are conducted using STATA SE 10.0. The results of all statistical tests are assumed to be significant if p values are less than 0.05.

Due to differences in the inclusion and exclusion criteria used in the two trials as well as differences in the interventions that are evaluated, the decision was made not to pool the results in a meta-analysis. Furthermore, there was a concern that pooling the results of these two studies may introduce a publication bias (Higgins &Green 2009).

6.4 Results

6.4.1. Evaluation of the effect of deprivation on healing using VenUS I

VenUS I recruited a total of 387 participants with venous leg ulcers, 195 of whom who were allocated to receive four layer bandages and 192 were allocated to receive short stretch bandages. The characteristics of the participants are shown below in table 6.2

Table 6.2 Baseline characteristics of VenUS I participants

	4LB n=195		**SSB n=192**	
Continuous variables	**n**	**Mean (SD) [Range]**	**n**	**Mean (SD) [Range]**
Patient characteristics				
Age (years)	195	71.9 (12.3) [25-97]	192	71.3 (14.1) [23-96]
Height (m)	192	1.7 (0.1)	192	1.7 (0.1)
Weight (kg)	192	80.6 (19.4) [33.1-139.7]	185	79.0 (20.3) [38.1-142.4]
Townsend score	184	0.5 (3.2) [-6.3-6.5]	181	0.5 (3.4) [-6.78-6.88]
History of ulceration				
Duration (years since onset)	190	3 [0-60]	182	4 [0-75]
Episodes since onset	190	2 [0-50]	185	2 [0-64]
Leg and ulcer characteristics				
Ankle circumference (cm)	193	23.8 (2.1) [16.2-34.0]	187	23.9 (2.9) [16-32.3]
Duration (months)	193	3 [0-456]	184	3 [0-768]
Area (cm^2)	194	3.8 [0.2-254.6]	192	3.8 [0.4-143.9]
ABPI	187	1.1 (0.15) [0.8-1.9]	186	1.0 (0.14) [0.8-1.6]

The baseline characteristics of VenUS I participants have been shown to be well matched, irrespective of whether continuous or categorical variables were examined (Iglesias et al. 2004). The addition of the Townsend deprivation score failed to indicate any differences between the mean values in each of the trial arms. Mean values, standard deviations and ranges of all variables in both arms were shown to be comparable.

In table 6.3 below further baseline characteristics of categorical values are shown.

Table 6.3 Further baseline characteristics of VenUS I participants (categorical variables)

Categorical variables	**4LB n=195**		**SSB n=192**		**Total**	
Patient characteristics	n	%	n	%	n	%
Male	79	40.5	80	41.7	159	41.1
Female	116	59.5	112	58.3	228	58.9
Ulcerated right leg	88	45.1	82	42.7	170	43.9
Ulcerated left leg	107	54.9	108	56.3	215	55.5
Fully mobile	123	63.1	115	60.0	238	61.5
Walks with assistance	72	36.9	70	36.5	142	36.7
Immobile	0	0	3	1.6	3	0.8
Ankle mobility (full motion)	131	67.2	128	66.7	259	66.9
Ankle mobility (reduced motion)	59	30.3	58	30.2	117	30.2
Ankle mobility (fixed)	3	1.5	2	1.0	5	1.3
Townsend deprivation fifth rank						
1 (least deprived)	29	14.9	34	17.7	63	16.3
2	35	17.9	25	13.0	60	15.5
3	38	19.5	42	21.9	80	20.7
4	35	17.9	38	19.8	73	18.9
5 (most deprived)	47	24.1	42	21.9	89	23.0
Missing	11	5.7	11	5.7	22	5.7
Leg and ulcer characteristics						
Sloughy ulcer	130	67.0	108	56.3	238	61.5
Granulating ulcer	127	65.1	115	59.9	242	62.5
Epithelialising ulcer	27	13.8	25	13.0	52	13.4
Eczematous skin	59	30.3	49	25.5	108	27.9
Macerated skin	31	15.9	26	13.5	57	14.7
Cellulitis skin	15	8.2	15	7.8	30	7.8
Lipodermatosclerosis skin	88	45.1	86	44.8	174	55.0
Stratifying variables						
Ulcerated area ≤ 10 cm^2	158	81.0	158	82.3	316	81.7
Ulcerated area > 10 cm^2	37	19.0	34	17.7	71	18.3
Had previous ulcer on the trial leg	115	59.0	114	59.4	229	59.2
First episode of ulceration on trial leg	80	41.0	78	40.6	158	40.8
Ulcer duration ≤6 months	138	70.8	143	74.5	281	72.6
Ulcer duration >6 months	57	29.2	49	25.5	106	27.4

In table 6.3 above the Townsend deprivation score is examined as a fifth to explore whether there are any differences in the proportion within each fifth between trial arms. These results showed no significant differences between the proportions of patients in any deprivation fifths between the two arms, nor in the proportion of participants with a missing Townsend deprivation fifth in either study arm.

6.4.2 Comparison of the VenUS I and G.P. database practice population

Shown below in table 6.4 is a comparison of the demographic characteristics of VenUS I participants and the prevalent venous leg ulcer population of the GPRD and THIN databases. The trial population is shown to be broadly comparable to the general practice venous leg ulcer population across a range of patient characteristics. Slight differences between the two populations are observed. The trial population is shown to contain slightly fewer women (60% *vs* 62.3-62.4), was slightly younger (women 74.7 *vs* 76.7-76.7) and has a higher proportion living in more deprived areas than the general practice leg ulcer population (23% *vs* 15.8).

Table 6.4 Comparison of the primary care and VenUS I populations

Patient characteristic	THIN database prevalent venous leg ulcer population	GPRD prevalent venous leg ulcer population*	VenUS I population
Female, N (%)	9420 (62.4)	12889 (62.3)	116 (60.0)
Mean age (SD), Median, range, in years Female			
	76.8 (13.1) 80, 18-109	76.7 (13.2) 80, 18-109	74.7 (11.5) 76, 36-96
Male			
	69.2 (15.1) 72, 18-102	69.4 (15.0) 72, 18-103	67.2 (14.2) 69, 23-97
Townsend deprivation fifth rank, N (%)			
1 (least deprived)	3207 (21.2)	-	63 (16.3)
2	3358 (22.2)	-	60 (15.5)
3	3483 (23.1)	-	80 (20.7)
4	3200 (21.2)	-	73 (18.9)
5 (most deprived)	2387 (15.8)	-	89 (23.0)
Missing	1136 (7.5)	-	22 (5.7)

*The GPRD did not contain any patient level SES data when this study was conducted.

The relationship between and the primary outcome of complete ulcer healing is first evaluated by performing bivariate analyses. The results of these analyses are shown below in table 6.5.

Table 6.5 Bivariate relationship of variables included in the VenUS I and the primary outcome of complete ulcer healing

Variable	Exp (βi)Hazard Ratio	Exp (βi)95% C.I.	p value
Episodes	0.96	0.93-0.98	0.003
Weight	0.99	0.98-0.99	0.024
Ln (area)	0.66	0.60-0.74	<0.001
Ln (duration)	0.97	0.96-0.98	<0.001
Ankle mobility	1.86	1.44-2.41	<0.001
Centre			
North Yorkshire	1		
Leeds	1.22	0.90-1.66	0.207
Cumbria	2.62	1.88-3.65	<0.001
West London	1.32	0.85-2.06	0.217
Southport	1.16	0.72-1.88	0.538
Falkirk	1.01	0.54-1.90	0.978
Calderdale	1.42	0.68-2.94	0.348
East London	0.80	0.35-1.83	0.596
Newmarket	0.74	0.27-2.02	0.555
Townsend deprivation fifth rank			
1 (least deprived)	1		
2	1.04	0.70-1.55	0.830
3	1.06	0.74-1.54	0.745
4	0.97	0.66-1.43	0.870
5 (most deprived)	0.96	0.66-1.38	0.819
Townsend deprivation score	0.99	0.96-1.02	0.679

The bivariate relationship between deprivation and the primary outcome of VenUS I, complete leg ulcer healing, is investigated by examining the influence of the Townsend deprivation index in two ways; as a score and as a fifth. The results from this bivariate analysis is shown above in table 6.5 and demonstrate that deprivation, whether measured using the Townsend deprivation fifth or as a score, showed no evidence for a relationship with the primary outcome of healing. All other variables included in the bivariate analysis were found to have a statistically significant relationship with leg ulcer healing.

Further examination of the relationship between deprivation and healing was undertaken using Cox regression methods. This allows examination of the relationship between multiple predictive variables and the primary outcome of healing to replicate the results of the primary analysis of the VenUS I trial. Separate Cox proportional hazard models are created so that the effect of deprivation could be examined, first as a rank and second as a continuous score. The results of Model one, shown in table 6.6 below, displays the parameters and the hazard ratios for each of the variables included in the model examining the effect of the Townsend deprivation Index as a fifth. None of the parameters of the hazard ratios for any of the Townsend deprivation fifths were shown to be predictive of healing, or indeed of non-healing. The inclusion of the deprivation fifth

does not change the magnitude or the direction of the effect of any of the original parameters included in the model.

Table 6.6 Original model with Townsend deprivation fifth rank

Variable	Co-efficient βi	Standard error of the co-efficient SE(βi)	Hazard Ratio Exp (βi)	95% CI Hazard ratio, exp (βi)
Arm	-0.32	0.12	0.75	(0.59-0.97)
Episodes	-0.04	0.02	0.97	(0.93-1.00)
Weight	-0.01	0.00	0.99	(0.98-1.00)
Ln (area)	-0.29	0.06	0.74	(0.65-0.83)
Duration	-0.02	0.01	0.98	(0.97-1.00)
Ankle mobility	0.35	0.14	1.40	(1.05-1.44)
North Yorkshire	1			
Leeds	0.02	0.17	1.06	(0.74-1.51)
Cumbria	0.74	0.18	2.12	(1.48-3.05)
West London	0.51	0.25	1.69	(0.98-2.92)
Southport	-0.09	0.26	0.91	(0.54-1.53)
Falkirk	-0.16	0.33	0.97	(0.49-1.95)
Calderdale	0.42	0.38	1.51	(0.71-3.21)
East London	-0.73	0.47	0.51	(0.20-1.34)
Newmarket	-0.03	0.52	1.01	(0.36-2.80)
Townsend deprivation rank				
1 (least)	0			
2	-0.07	0.27	1.16	(0.75-1.78)
3	-0.22	0.24	1.04	(0.71-1.54)
4	-0.43	0.25	0.96	(0.64-1.44)
5 (most)	-0.25	0.23	1.06	(0.70-1.57)

Model two, shown below in table 6.7, replicated the original analyses of the VenUS I and added the Townsend deprivation index as a score to examine its association with the primary outcome of leg ulcer healing. The hazard ratio and the corresponding 95% confidence interval of the estimate (1.0; 95% C.I. 0.96-1.04) indicated that there was no statistically significant association between healing and the Townsend deprivation score. In the second model, these results demonstrated that the addition of the Townsend deprivation score did not change the magnitude or direction of effects of any of the other included model parameters.

Table 6.7 Model 2 Original model with Townsend deprivation score

Variable	βi	SE(βi)	Exp (βi)	95% CI, exp (βi)
Arm	-0.30	0.13	0.74	(0.58-0.95)
Episodes	-0.04	0.02	0.97	(0.94-1.00)
Weight	-0.01	0.00	0.99	(0.99-1.00)
Ln (area)	-0.30	0.06	0.74	(0.66-0.84)
Duration	-0.02	0.01	0.98	(0.97-1.00)
Ankle mobility	0.34	0.14	1.40	(1.06-1.44)
North Yorkshire	1			
Leeds	-0.03	0.18	0.97	(0.69-1.37)
Cumbria	0.73	0.18	2.08	(1.48-3.05)
West London	0.49	0.27	1.64	(0.96-2.80)
Southport	-0.09	0.26	0.92	(0.55-1.55)
Falkirk	-0.09	0.36	0.92	(0.47-1.81)
Calderdale	0.40	0.38	1.49	(0.71-3.15)
East London	-0.73	0.48	0.48	(0.18-1.234)
Newmarket	-0.03	0.52	0.97	(0.35-2.68)
Townsend deprivation score	0.00	0.02	1.00	(0.96-1.04)

6.4.2 Evaluation of the effect of deprivation on adverse events using VenUS I

Finally, the results of adverse events were stratified by deprivation rank to assess if there were any differences in the proportion of types of adverse events or total numbers of adverse events. In keeping with the original analyses separate analysis of adverse events classed as related to treatment and those that unrelated to treatment were conducted. In the case of the VenUS I trial infections were not reported separately as an adverse event outcome. Table 6.8 below shows the results of the stratification for unrelated and related adverse events respectively. These results show that there was no clear linear association between any of the unrelated adverse events and membership of Townsend deprivation rank. Furthermore, no trend was observed in the overall number of unrelated adverse events experienced by patients in VenUS I.

Table 6.8 Results of adverse events unrelated to treatment stratified by Townsend deprivation fifth

Adverse event	4LB	SSB	Total
Total number of patients with adverse events	33	39	72
1 (least deprived)	7 (21.2)	4 (10.3)	11 (15.3)
2	6 (18.2)	5 (12.8)	11 (15.3)
3	8 (24.2)	5 (12.8)	13 (18.3)
4	7 (21.2)	11 (28.2)	18 (25.0)
5 (most deprived)	4 (12.2)	11 (28.2)	15 (20.8)
Missing	1 (3.0)	3 (7.7)	4 (5.3)
Total No. of adverse events	52	69	121
1 (least deprived)	11 (21.2)	6 (8.7)	17 (14.1)
2	9 (17.3)	9 (13.0)	18 (14.9)
3	13 (25.0)	8 (11.6)	21 (17.4)
4	12 (23.0)	23 (33.4)	35 (28.9)
5 (most deprived)	5 (9.6)	19 (27.5)	24 (19.8)
Missing	2 (3.9)	4 (5.8)	6 (4.9)

Next adverse events deemed to be related to treatment were stratified by Townsend deprivation fifth, to examine any potential relationships that may exist. These results are shown below in table 6.9. These results do not demonstrate any consistent linear relationship between deprivation fifth ranks and proportions of patients experiencing adverse event related to treatment in the trial arms or in the total results.

Table 6.9 Adverse events potentially related to compression treatment

Adverse event	4LB	SSB	Total
Total number of patients with adverse events	76	91	167
1 (low deprivation)	15 (19.7)	10 (10.9)	25 (15.0)
2	10 (13.2)	11 (12.1)	21 (12.6)
3	10 (13.2)	18 (19.8)	28 (16.8)
4	16 (21.0)	21 (23.1)	37 (22.2)
5 (high deprivation)	20 (26.3)	24 (26.4)	44 (26.3)
Missing	5 (6.6)	7 (7.7)	12 (7.1)
Total no. of adverse events	255	337	592
1 (low deprivation)	62 (24.3)	67 (19.9)	129 (21.8)
2	38 (14.9)	24 (7.1)	62 (10.5)
3	39 (15.3)	69 (20.5)	108 (18.2)
4	30 (11.8)	61 (18.1)	91 (15.4)
5 (high deprivation)	67 (26.3)	94 (27.9)	161 (27.2)
Missing	19 (7.5)	22 (6.5)	41 (6.9)

6.4.3 Evaluation of the effect of deprivation on healing using VenUS II

Table 6.10 below shows the baseline characteristics of the participants in each of the three arms of the VenUS II trial. There were differences in the distribution of many of the baseline characteristics between the three treatment arms which were identified in the previous analyses (Dumville et al. 2009). Specifically, differences were observed in gender distributions between the hydrogel and larval groups with more men in the hydrogel group. Differences were also observed in ulcer duration with greater numbers of participants with ulcers of less than six months duration in the bagged ulcer group compared to the other two groups. Further differences were observed in ulcer size between groups with larger ulcers being observed in the bagged ulcer group compared to the other two groups.

This new analysis demonstrated baseline imbalances in the proportion of participants within each Townsend deprivation fifth between the three trial arms. Proportions of participants were broadly comparable between the bagged larvae and hydrogel groups. The loose larvae groups tended to have lower numbers of patients in both the highest and lowest levels of deprivation with greater concentrations of patients in fifths two and four. However, there appeared to be little difference between the mean Townsend scores within each group

Table 6.10 Baseline characteristics of the VenUS II population

	Loose larvae (n=94)	Bagged larvae (n=86)	Hydrogel (n=87)	Total (n=267)
Male, N (%)	36 (38.3)	29 (33.7)	44 (50.6)	109 (40.8)
Female, N (%)	58 (61.7)	57 (66.3)	43 (49.4)	158 (59.2)
Age (years)				
Mean (SD)	74.1 (12.9)	73.5 (12.2)	74.3 (12.8)	74.0 (12.6)
Median (range)	76.6 (20.9, 94.2)	76.5 (32.7, 94.9)	75.4 (35.8, 93.5)	76.0 (20.9, 94.9)
Townsend deprivation fifth, N (%)				
1 (low deprivation)	13 (13.8)	16 (18.6)	18 (20.7)	47 (17.6)
2	27(28.7)	16 (18.6)	14 (16.1)	57 (21.3)
3	19 (20.2)	24 (27.9)	21 (24.1)	64 (24.0)
4	21 (22.3)	14 (16.3)	15 (17.2)	50 (18.7)
5 (high deprivation)	12 (12.8)	15 (17.4)	18 (20.7)	45 (16.9)
Missing	2 (2.2)	1 (1.2)	1 (1.2)	4 (1.5)
Townsend deprivation score				
Mean (SD)	-0.2 (3.0)	0.1 (3.1)	-0.3 (3.2)	-0.7 (3.1)
Weight (kg)				
Mean (SD)	79.7 (24.3)	76.7 (21.4)	87.0 (27.6)	81.1 (24.9)
Median (range)	73.6 (38.0, 158.0)	73.1 (44.5, 164.0)	82.7 (42.7, 172.0)	76.4 (38.0, 172.0)
Missing, N (%)	4 (4.3)	6 (7.0)	4 (4.6)	14 (5.2)
MOBILITY, N (%)				
Walks freely	48 (51.1)	42 (48.8)	46 (52.9)	136 (50.9)
Walks with difficulty	42 (44.7)	36 (41.9)	33 (37.9)	111 (41.6)
Immobile	3 (3.2)	7 (8.1)	6 (6.9)	16 (6.0)
Missing	1 (1.1)	1 (1.2)	2 (2.3)	4 (1.5)

Table 6.11 below shows a comparison of the patient characteristics of VenUS II with the patient characteristics of the GPRD and THIN databases. The VenUS II population was shown to be broadly similar to the populations from the two primary care databases. The only differences observed were a slightly lower proportion of women in VenUS II and slightly lower numbers of patients in the most deprived category.

Table 6.11 Comparison between primary care patients and VenUS II participants

Patient characteristic	THIN database prevalent venous leg ulcer population	GPRD prevalent venous leg ulcer population*	VenUS II trial population
Female, N (%)	9,420 (62.4)	12889 (62.3)	158 (59.2)
Mean age (SD), Median, range, in years			
Female	76.8 (13.1) 80, 18-109	76.7 (13.2) 80, 18-109	75.6 (11.5) 78.1, 35-94.9
Male	69.2 (15.1) 72, 18-102	69.4 (15.0) 72, 18-103	71.7 (13.7) 74.5, 20.9-94.1
Townsend deprivation rank, N(%)			
1 (low deprivation)	3207 (21.2)	-	47 (17.6)
2	3358 (22.2)	-	57 (21.3)
3	3483 (23.1)	-	64 (24.0)
4	3200 (21.2)	-	50 (18.7)
5 (high deprivation)	2387 (15.8)	-	45 (16.9)
Missing	1136 (7.5)	-	4 (1.5)

*The GPRD did not contain any patient level SES data when this study was conducted.

First, assessment of the relationship between deprivation and healing was conducted by analysing the bivariate relationship between variables included in the Cox regression models and the primary outcome of complete leg ulcer healing. The results of these analyses are shown below in table 6.12.

Table 6.12 Bivariate relationships between variables included in the VenUS II analysis and the outcome of healing

Variable	Exp (βi)Hazard Ratio	Exp (βi)95% C.I.	p value
Log area, cm2	0.55	0.46-0.66	<0.001
Log duration, months	0.56	0.48-0.66	<0.001
Ulcer type ABPI ≥0.8 high compression : ABPI 0.6 to 0.8	1.08	0.65-1.80	0.776
ABPI ≥0.8 low compression : ABPI 0.6 to 0.8	0.92	0.62-1.35	0.661
Townsend deprivation rank 1 2 3 4 5	 1 1.26 1.06 0.83 0.92	 0.74-2.15 0.54-1.56 0.46-1.50 0.51-1.66	 0.394 0.750 0.535 0.778
Townsend deprivation score	0.99	0.96-1.02	0.290
Centre	1.36	0.75-2.48	0.307

The results of the bivariate analysis showed that the only variables found to have a statistically significant relationship with leg ulcer healing were leg area and duration. Hazard ratios of 0.55 and 0.56 respectively indicated that participants with larger ulcer area and longer ulcer duration were at least 50% less likely to heal compared with participants with smaller ulcers and ulcers of more recent duration.

Second, two new models were created to investigate the effect of deprivation on the outcome of healing using the original analysis of VenUS II. The first model explored deprivation as a fifth with the full adjusted analysis of the original model and the results showing the values of the parameters of the explanatory variables and corresponding hazard ratios of the parameters included in the model are shown below in table 6.13.

The results of model one demonstrated that the Townsend deprivation index, measured as a fifth of the original score, showed no association with the primary outcome of healing. In all cases the confidence intervals of the estimates of the hazard ratio for each deprivation fifth compared to rank one showed no association with the outcome of healing. The addition of the deprivation variable did not change the magnitude or the direction of the effect of any of the other parameters included in the model, with duration and ulcer size still observed to be statistically associated with leg ulcer healing.

Table 6.13 Model 1 VenUS II original analysis with Townsend deprivation fifth

	Parameter estimate	Standard error	Hazard ratio (95% CI)	p-value
Larvae : hydrogel	0.225	0.201	1.252 (0.844, 1.856)	0.264
Log ulcer area	-0.560	0.099	0.571 (0.471, 0.693)	<0.0001
Log ulcer duration	-0.559	0.087	0.567 (0.482, 0.678)	<0.0001
Ulcer type ABPI ≥0.8 high compression : ABPI 0.6 to 0.8	0.044	0.277	1.045 (0.608, 1.798)	0.873
ABPI ≥0.8 low compression : ABPI 0.6 to 0.8	-0.091	0.210	0.912 (0.605, 1.377)	0.663
Townsend deprivation fifth rank 1 (low)	1			
2	0.170	0.277	1.185 (0.688, 2.042)	0.540
3	-0.240	0.277	0.787 (0.457, 1.355)	0.387
4	0.086	0.306	1.089 (0.597, 1.984)	0.780
5 (high)	-0.214	0.317	0.807 (0.433, 1.503)	0.500
Centre				0.576

The second model was created to explore the effect of deprivation on the primary outcome of healing. Deprivation was explored using the Townsend deprivation score in addition to the parameters included in the original model. These results are shown below in table 6.14 indicating that there were no statistically significant associations observed between the outcome of healing and the Townsend deprivation score. The results from Model one and two were consistent with the results from the original analyses as performed by Dumville et al. (2009).

Table 6.14 Model 2 original analysis with Townsend deprivation score

	Parameter estimate	Standard error	Hazard ratio (95% CI)	p-value
Larvae : hydrogel	0.211	0.293	1.235 (0.833, 1.831)	0.293
Log ulcer area	-0.555	0.096	0.574 (0.475, 0.693)	<0.0001
Log ulcer duration	-0.541	0.086	0.582 (0.492, 0.689)	<0.0001
Ulcer type ABPI ≥0.8 high compression : ABPI 0.6 to 0.8	-0.004	0.273	0.996 (0.583, 1.703)	0.873
ABPI ≥0.8 low compression : ABPI 0.6 to 0.8	-0.089	0.209	0.912 (0.607, 1.379)	0.663
Townsend deprivation score	-0.029	0.306	0.971 (0.915, 1.031)	0.338
Centre				0.576

6.4.4 Evaluation of the relationship between SEP and adverse events in VenUS II

In the original analysis the primary exploration of the number of adverse events was undertaken using a negative binomial approach. Two models were undertaken; the first model compared the number of events in larval therapy groups with the number in the hydrogel group using a negative binomial approach and found no significant difference (p=0.22). The second model undertaken

was a further negative binomial regression which also adjusted for the baseline prognostic factors in the trial. The results of this second analysis also failed to produce a statistically significant relationship (p=0.10). In this current analysis Townsend score was also added to the negative binomial regression model in addition to the prognostic factors that had been included earlier. The results of this current analysis also failed to demonstrate a statistically significant result (df 9, p=0.07) suggesting that the Townsend deprivation index score was not statistically significantly associated with the amount of adverse events reported during the VenUS II trial.

The results of adverse events published previously were stratified by Townsend deprivation fifth and examined descriptively to examine associations between these two variables. Adverse events examined included the total number of participants with one or more adverse events, the number of events classed as serious and the number of patients with MRSA at baseline. The full results of this stratification can be seen below in table 6.15.

Table 6.15 Adverse events in the VenUS II stratified by deprivation

	Combined larvae N=180	Hydrogel N=87	Total N=267
Number of participants with one or more adverse events	93 (51.7)	38 (43.7)	131 (49.1)
1 (low deprivation)	14 (15.1)	5 (13.2)	19 (14.5)
2	26 (28.0)	7 (18.4)	33 (25.2)
3	23 (24.7)	8 (21.1)	31 (23.6)
4	16 (17.2)	9 (23.7)	25 (19.1)
5 (high deprivation)	13 (13.9)	8 (21.1)	21 (46.7)
Missing	1 (1.1)	1 (2.5)	2 (5.0)
Total number of adverse events	236	104	340
Event classed as serious	33 (13.9)	14 (13.5)	47 (13.8)
1 (low deprivation)	4 (12.1)	3 (21.4)	7 (14.9)
2	9 (27.3)	1 (7.0)	10 (25.5)
3	12 (36.4)	0	12 (21.3)
4	5 (15.2)	5 (35.7)	10 (21.3)
5 (high deprivation)	3 (9.0)	5 (35.7)	8 (17.0)
Missing	0	0	0
Number of participants with MRSA at baseline	12 (12.9)	6 (6.9)	18 (6.7)
1 (low deprivation)	3 (25.0)	1 (16.7)	4(22.2)
2	2 (16.7)	2 (33.3)	4 (22.2)
3	4 (33.3)	0	4 (22.2)
4	2 (16.7)	3 (50.0)	5 (27.8)
5 (high deprivation)	1 (8.3)	0	1 (5.6)
Missing	0	1 (2.5)	2 (5.0)
Number of who developed an infection	49 (27.2)	27 (26.0)	76 (22.4)
1 (low deprivation)	5 (10.2)	4 9 (14.9)	9 (11.9)
2	24 (49.0)	9 (33.3)	33 (43.4)
3	5 (10.2)	7 (25.9)	12 (15.8)
4	12 (24.6)	2 (7.4)	14 (18.4)
5 (high deprivation)	3 (6.0)	5 (18.5)	8 (10.5)
Missing	0		0

These stratified results examining the relationship between the number of adverse events and Townsend deprivation fifth membership were consistent with the earlier results of the negative binomial regression analyses in also finding no association between deprivation and adverse events.

Finally, no relationship with Townsend deprivation rank was observed with adverse events classed as serious as well as the number that developed an infection and those that had MRSA at baseline.

6.5 Discussion

6.5.1 Key statement of findings

The analyses in this chapter were undertaken to explore three key aims. First, to assess whether patient's socio-economic position had any relationship with healing. Second, to evaluate whether there was any relationship between participant's socio-economic position and adverse events. Third, to find out how representative trial patients are of leg ulcer patients being treated in general practice.

The primary analyses of both VenUS I and II were replicated and an indicator of area-level deprivation, as a proxy for individual socio-economic position, was added to the original models created to examine time to leg ulcer healing. The indicator of deprivation, the Townsend deprivation index, was evaluated in two different forms; as a Townsend deprivation score and as a rank of the score. The inclusion of these two additional explanatory variables into the original models was not found to change the magnitude or direction of the effect of any of the original covariates included in the model. The Townsend deprivation index, whether examined as a score or as a fifth rank, was not found to be statistically associated with time to healing in either clinical trial. Additionally, the results of adverse events did not show any association with the deprivation fifth rank of the trial participants.

The results have shown that although leg ulcer patients are more likely to be resident in deprived areas than the population seeking care from practitioners that contribute to the THIN database, this was not associated with leg ulcer healing. The findings of this study demonstrate that if patients are provided with high quality leg ulcer care there is no indication that socio-economic factors make a large contribution to patient relevant outcomes such as healing and adverse events. This is despite lower socio-economic position increasing the risk of developing incident and prevalent venous and prevalent arterial leg ulcers.

Analyses conducted in the previous chapter provided a detailed summary of the characteristics of leg ulcer patients consulting in primary care based on data from two large nationally representative primary care databases. This has enabled the representativeness of two leg ulcer trial populations to be compared to two different national samples of leg ulcer patients attending primary care for treatment. The leg ulcer trial participants were not found to have any marked differences from the general practice populations of either database in terms of age or gender, or deprivation distributions. These results indicate that there may not be great differences in the demographics of

leg ulcer patients seeking treatment in primary care and those being treated in leg ulcer clinics or by community nurses, the source of participant recruitment to the two VenUS trials.

6.5.2 Strengths and weaknesses of the current work

Two key strength of this study include the large sample sized used and the use of randomised trial data to study the investigation of the relationship of socio-economic position and leg ulcer healing and adverse events. Two of the largest randomised clinical trials of treatment for leg ulceration conducted in the UK were used which contain data from over 600 patients. All data used in these analyses were collected prospectively, including the postcodes from which the Townsend scores were derived so would not be subject to recall error. As the analyses used randomised trial data, the chance of any of the results being due to confounding was minimised, as key variables known to be associated with healing, including ulcer duration and size (Margolis et al. 2004a), were controlled for.

A further strength of this work was that the socio-economic position measure used, the Townsend deprivation index, was calculated from the participants current area of residence at study registration using data collected from the 2001 census. The methods used to construct Townsend values for all participants were identical to those used to calculate values for patients included in the THIN database. As patients were recruited to the trials between 1999 and 2004, it is unlikely that the area based characteristics used to construct the Townsend deprivation index would have changed greatly over this time period.

Comparisons of the representativeness of trial patients were conducted using the results of prevalence from two of the largest general practice databases in the UK. There are however several limitations to the current work. First, it is acknowledged that only a limited range of patient characteristics from the trial participants could be compared to data from the general practice population. Far greater quantities of patient data are collected during a clinical trial compared to usual clinical practice, regardless of which practitioners undertake management of a leg ulcer patient. The available data do suggest that the trial population is fairly representative of the wider leg ulcer population being treated in general practice. However, differences in other factors, particularly those that are known to prognostic of leg ulcer healing, such as leg ulcer size and duration, which were not able to be compared in this study between trial and general practice populations cannot be ruled out.

A further limitation of this work is that, although the trial population could be compared with the large numbers of patients treated in general practice, the participants included in these trials were recruited from nurse led clinics and community nursing caseloads. Burden of disease studies

undertaken in the community nursing managed leg ulcer population of the UK were not available. Therefore differences in the severity or demographic characteristics between the leg ulcer populations treated within general practice cannot be excluded. However, as self referral to community nurses is not the norm in the UK, it would be unlikely that these patients would not have first been treated within general practice meaning that there would be records for these patients. The evidence from the general practice referrals data in the previous two chapters showed that only a small proportion of leg ulcer patients had a record of being referred to leg ulcer clinics or community nurses.

6.5.3 Strengths and weaknesses in relation to other studies

Only one previous study has evaluated the role of socio-economic position as a potential effect modifier in the leg ulcer healing process. This earlier work was a case series examining the healing outcomes of a series of 168 patients with venous leg ulceration treated at a specialist community leg ulcer clinic (Franks et al. 1995a). In the Franks(1995a) study the effect of two different elements of socio-economic position on the outcome of healing were evaluated, these being occupational social class and lack of central heating, which may be indicative of material deprivation. This study found that there was no effect of occupational social class on healing when adjusted for baseline prognostic factors such as ulcer size, duration and patient mobility. However, lack of central heating was found to have a statistically significant relationship with delayed healing OR 2.27 (95% C.I. 1.11-4.55) even after adjustment for baseline prognostic factors, including ulcer duration and size. In the current study lack of central heating was not measured so the results of the two studies cannot be compared in relation to this factor.

A further limitation of the current analysis in relation to other studies is that the current analysis has been restricted to the examination of proxy measures of individual deprivation rather than actual measures of individual deprivation as used by Franks (1995a). There is therefore the possibility that the study may not have accurately identified patient's deprivation status and have been subject to ecological fallacy. Despite this concern, area level deprivation has been shown to be associated with a wide range of adverse health outcomes.

It is of further interest to note that the leg ulcer population included in the analysis conducted by Franks et al. (1995a) had all received high quality leg ulcer care, having had their ABPI measured and had been treated with compression therapy if there were no contraindications highlighted. In the current analyses I have used the results from two randomised controlled trials to replicate the findings of Franks et al.(1995a) and so minimised the likelihood of bias being present in the findings of the current study. Despite differences in the methods used by Franks et al.(1995a) their

results and the results of this current study both highlight that the provision of high quality care can overcome the health inequalities that are evident in the development of leg ulcers.

The results of the current study contrast with the earlier results reported by Bagger et al. (2004) who found a relationship between MRSA in post-operative coronary artery bypass surgical wounds and deprivation. In the current study no such association was seen. It was previously noted by Dumville et al. (2009) that rates of MRSA detected in VenUS II were lower than that observed in studies of other wound types. The sample size of the study conducted by Bagger et al. (2004) was in excess of 1700 patients, so had a greater power to detect differences in rates of infection by socio-economic position than the current analyses.

Statistical comparisons between the characteristics of patients in the trials and databases were not undertaken as results were likely to show statistically significant differences due to the large numbers of prevalent patients in the primary care databases. As an example, a difference of a mean age of one year between the trial population and database populations would result in a statistically significant difference, even though there is no suggestion that this difference would have any clinical significance.

To my knowledge, this is the first time socio-economic position of leg ulcer patients have been examined in a clinical trial. As the earlier work undertaken in chapter five had demonstrated that there were differences in the development and management of leg ulceration by patients SES it was important to examine whether these differences manifested in different patient outcomes. Second it was important to examine whether clinical trial populations are representative of the wider leg ulcer population. In other disease areas, such as cancer, it has been documented that particular members of the population, including ethnic minorities, older adults and the socio-economically deprived, are underrepresented in recruitment to clinical trials (Ford et al. 2008). This does not appear to be the case in the venous ulcer studies investigated.

6.5.4. Meaning of the study

These results suggest that the application of a standardised high quality programme of leg ulcer treatment has the ability to eradicate the health inequalities that are evident in the development of this condition, as people of lower socio-economic position are not shown to be at lower odds of achieving leg ulcer healing. The results further demonstrate that there is unlikely to be associations with adverse treatment outcomes and deprivation for leg ulcer patients.

This current analysis has also shown that there are considerable variations in the management of patients within a clinical trial setting compared to management within general practice. In the trials

evaluated in the current chapter, as well as the earlier published work by Franks et al. (1995a), patients were found to be receiving a standard of care that contrasts greatly with that reported in general practice. The results of reported leg ulcer management in primary care, as shown in chapters four and five, indicated that not all leg ulcer patients received Doppler ultrasound assessment or were provided with compression bandages as a first line therapy. The findings of this study indicate that there are clear benefits to all patients of a standardised evidence based management approach to leg ulcer care that negate the health disparities encountered in disease development. These analyses further demonstrates that leg ulcer trials can recruit representative patient groups as there is no evidence of any systematic exclusion from these trial populations that has been observed in clinical trials conducted in other disease areas (Bartlett et al. 2005).

7.0 Final discussions and conclusions

7.1 Introduction

In this final chapter I will attempt to answer the following questions; (i) Has the thesis achieved what it set out to do and what does it contribute to knowledge? (ii) How original was the approach? (iii) How does this thesis confirm or challenge other research? (iv) What were the methodological strengths and limitations? (v) What are the research policy and practice implications of these findings?

7.2 Has the thesis achieved what it set out to do and how does it contribute to knowledge?

The aims of the thesis were ;

- To examine the influence of socio-economic position on the incidence and prevalence of leg ulceration.
- To examine the diagnostic assessment, treatment and referral patterns of patients presenting to general practice with leg ulcers and to explore potential differences by patient factors (age, sex, socio-economic position) and by practitioner related factors (practice list size and practice level deprivation).
- To explore the impact of socio-economic position upon healing and likelihood of adverse events and to describe the socio-economic position of leg ulcer trial participants.

The exploration of socio-economic position began by creating estimates of the incidence and prevalence of leg ulceration with a database diagnosis of venous, arterial and mixed venous arterial diagnoses using two of the largest UK primary care databases available. These results showed that comparable rates of incidence of venous and arterial leg ulcers were available in both databases from 2000 onwards and prevalence of venous and arterial leg ulcers from 2001 onwards. No formal testing of mixed venous arterial leg ulcers was performed due to the small numbers of patients diagnosed with this form of leg ulceration. It was important to derive my own estimates of incidence as no previous studies were found that had investigated the relationship of socio-economic factors and leg ulcer development. Although leg ulcer prevalence and duration had previously been shown to be higher in lower socio-economic position leg ulcer patients, no investigation of relationship with incidence had been performed. Therefore, whilst it was hypothesised that socio-economic factors may contribute to the development of leg ulcers, there was no evidence to affirm this.

The results of analyses conducted in chapter five showed that socio-economic position, measured using Townsend deprivation fifth rank, was associated with higher rates of incident and prevalent venous leg ulcers and higher rates of prevalent arterial leg ulcers. The results of my analysis further showed that older age was associated with higher rates of database diagnosed venous, arterial and mixed leg ulcers. Female gender was associated with higher incidence and prevalence rates of venous leg ulcers in contrast to results for arterial leg ulcers where no gender relationships were observed and mixed venous arterial ulcers were no consistent relationship with gender was observed. These results provide new knowledge demonstrating that socio-economic position is responsible for significant variation in both incident and prevalent leg ulcer rates. These results clearly demonstrate that socio-economic position is a contributory causal factor in leg ulceration.

There are several ways in which a person's socio-economic position may have influenced the development of leg ulceration. First, it is possible that the results observed, that ulcers are observed more frequently in persons living of lower socio-economic position, are suggestive of a psychosocial pathway of leg ulcer development. Psychosocial explanations of health inequalities hypothesise that health inequalities are created by '*Economic and social circumstances affecting health through the physiological effects of their emotional and social meanings and the direct effects of material circumstances*' (Marmot &Wilkinson 2006).

A second co-contributory psychosocial pathway is related to the combination of stress and deprivation. Stress, in both chronic and acute forms, has been shown to slow the normal wound healing response in otherwise healthy adults (Kiecolt-Glaser et al. 1995). A circular pattern of mental health has been hypothesised whereby poor mental health is both a cause and a consequence of social, economic and environmental inequalities (Friedli 2009). One aspect of stress that has been particularly well studied is that of occupational stress. Work from the Whitehall studies has shown that persons of lower employment grade are more likely than those with higher grades to report higher levels of stress at work (Ferrie 2004). People working in jobs at lower grades were more likely to experience less autonomy in their working lives which has been shown to be associated with the development of a wide range of mental and cardiac diseases (Ferrie 2004). Furthermore, it has been shown that work stress is more likely to lead to lower grade employees developing the metabolic syndrome which may be a precursor to a wide variety of health problems (Chandola et al. 2006).

The results of the studies conducted in chapters three, four and five suggest that some degree of diagnostic misclassification of leg ulcer aetiology is present in both of the primary care databases examined. Comparison of rates from the GPRD and THIN databases provided no evidence to indicate the presence of differential misclassification in recent data. Evidence from previous studies

evaluating the diagnostic classification of leg ulcers suggest that non-venous leg ulcers account for at least 20% of all leg ulcers encountered in clinical practice (Cornwall et al. 1986; Callam et al. 1988; Moffatt et al. 2004; Clarke-Moloney et al. 2006; Vowden &Vowden 2009). The results of the studies conducted in chapter four and five suggest that less than 5% of all leg ulcers encountered in primary care and recorded in the database were non-venous in origin.

There are two likely implications of these diagnostic errors. First, it is likely that the relationship between socio-economic position and rates of non-venous leg ulcers has been underestimated. It is likely that significant relationships between socio-economic position and non-venous leg ulcer rates would be evident if sample sizes of these participants were larger. Despite these diagnostic uncertainties, these results clearly demonstrate that there are contextual effects on leg ulcers from area level deprivation. These are in addition to the previously demonstrated compositional effects that were reported by Moffatt et al.(2004) when individual measures of socio-economic position were used. Second, temporal differences in rates in each database may be the result of different patterns of coding leg ulcers rather than suggestive of changing epidemiology of leg ulcers. For this reason the impact of leg ulcer guidelines on leg ulcer rates cannot be determined.

Having established that there were health inequalities in the development of venous leg ulcers, the next step of my investigation was to establish if there were treatment related inequalities. Previous studies of leg ulcer management were descriptive in nature only and undertook only limited investigation of differences in management. I have used multilevel models to explore venous leg ulcer management which allowed the contribution of both patient and practice related factors to be examined. The advantage of using a multilevel approach in these analyses is that the relative contribution of both patient and practice level variables can be quantified and the results are less likely to be subject to the ecological fallacy e.g. variations attributed to patient characteristics when practice characteristics cause the variation.

The results from these analyses showed that few patients had a database record of receiving guideline recommended standards of diagnosis, initial treatment with compression and referral. The only aspect of management examined with a relationship to socio-economic position was the initial measurement of leg ankle brachial pressure index. Patients living in more deprived areas and those attending practices living in more deprived areas were less likely to have a record of having received a Doppler ultrasound assessment. These consistency of these results were particularly unexpected given that different measures of deprivation were used by the databases (e.g. area where patient lives *vs* area where practice is located) and were from different geographical areas, England only in the GPRD and nationally in the THIN database, and at different levels, patients *vs* practice. This lack of diagnostic evaluation of leg ulcer patients living in the more deprived areas is a credible

causal pathway to explain the higher rates of prevalence observed in venous leg ulcer patients living in more deprived areas, despite adjustment for other known risk factors including age and gender.

The provision of compression therapy or referrals to leg ulcer and non-leg ulcer specialists was not found to be associated with deprivation whether measured at either the patient or practice level. Limited availability of information from the databases means that the reasons for these findings can only be hypothesised. First, there may be issues related to various characteristics of management strategies. First, the diagnostic accuracy of Doppler ultrasound may be limited in some patients and the application of compression bandaging therapy may not be safe or effective in all patients (RCN 2006). Second, not all practitioners may have the necessary training or confidence to undertake Doppler assessments or apply compression bandages. Third, although the numbers of patients referred for surgical management of their leg ulcers appeared low, this may have introduced some degree of confounding by indication to the results. Patients who are referred early in management may not have had a full diagnostic evaluation in primary care as they were referred to another provider and would never have had the opportunity to be treated using compression bandages Finally, evidence suggests that not all even when patient's are provided with compression bandaging they are not always concordant as many find them bulky, painful and anaesthetic (Van Hecke et al. 2008).

These results provide evidence that some aspects of guideline recommended care for leg ulcers has improved in general practice since the introduction of the clinical practice guidelines in the late 1990's although not all patients were shown to be benefiting equally in these improvements. There may be patient and practice related factors that may conflate these management associations with deprivation that are not evident from database records, however there any unlikely to explain all of the variation related to socio-economic factors.

Finally, the results in chapters three, four and five have demonstrated that the identification of cases of chronic conditions using routinely collected primary care will be more accurate where there are clearly linked diagnostic tests and homogeneous prescribing strategies that will strengthen the relationship between clinical coding and the validity of the database diagnosis. The analyses undertaken have also shown that it is not unusual for leg ulcer patients to experience multiple underlying pathologies at different times. For conditions such as leg ulceration, where the reported use of diagnostic tests is inconsistent and prescribing strategies are hetereogenous, there is considerable uncertainty regarding the accuracy of leg ulcer diagnosis. Despite this uncertainty work undertaken by Margolis et al. (2002) has shown the coding of venous leg ulcers in the GPRD is valid, although without supporting clinical validation there is likely some degree of diagnostic error present.

Using routinely recorded health care data will involves a compromise between accuracy and ease of access. Despite these reservations regarding data quality and potential diagnostic misclassification, the results from the two databases were found to produce similar estimates of burden of disease and results of investigations of patient management. There are, therefore, unlikely to be systematic misclassification between the results from the GPRD and THIN databases.

The final study in the thesis demonstrated that deprivation has no relationship with leg ulcer healing or adverse events when leg ulcer patients are provided with standardised high quality care. The hypothesised pathways between stress, socio-economic position and wound healing were not evident in these results. There may be several reasons for this lack of association between socio-economic position and chronic wound healing compared to the strong evidence that is observed for an association between acute wound healing and stress. First, no measurement was made of any personality or psychological traits. It may be that these factors are more strongly related to stress or may mediate some of the relationship between socio-economic position and wound healing. Certain personality traits such as cynical hostility have been shown to be associated with poorer health even after adjustment for socio-economic position (Nabi et al. 2008). Second, known prognostic factors, such as wound size and duration may have a greater impact on wound healing in patients with chronic wounds such as leg ulcers independently of socio-economic factors. A third and final explanation may be that the study sample size was too small to find an effect should one be shown to exist. Although MRSA rates found in the VenUS II trial were low (6.7%), the rates observed by Bagger et al (Bagger et al. 2004) were lower (1.3%), indicating that a larger sample size may be needed to detect an effect in venous leg ulcer patients.

The results obtained in chapter six may not be generalisable to the general practice population for several reasons. First, it was evident that not all patients treated in general practice received the same standard of leg ulcer care as the trial participants. Second, there may be differences in patient concordance to therapies outside of a clinical trial setting that would the dilute treatment effects observed. Third, practice deprivation associations with management may further compound the effects of individual deprivation observed meaning that the real impact on patients may be greater than observed in the current study.

The two randomised controlled trials of interventions for leg ulceration were found to be broadly representative of the leg ulcer population identified in primary care. These data compared the gender, age (measured as mean and median) and deprivation fifth rank of trial and primary care database leg ulcer patients. No large differences were identified in any of the variables examined in this analysis Therefore, there did not appear to be any disparity between the included trial and at

need leg ulcer population. Quantification of the external validity of trial populations is essential to ensuring that effect estimates produced by trials will not be biased (Bartlett et al. 2005).

7.3 How original was the approach

Multiple approaches were used in the thesis to explore the role of socio-economic position in the development, management and outcomes of leg ulcer healing. These represent significant originality in terms of the methods used and data sources utilised to answer the thesis questions.

7.3.1 Use of primary care resources to examine the socio-economic relationships between leg ulcer burden and management.

The methods of analysis undertaken in this thesis were significantly influenced by the earlier methods of Margolis et al (2002). This work showed the potential for routinely collected primary health data to answer questions of importance to public health and health services research for people with leg ulcers. Although primary care data has been used previously to examine leg ulcer burden and management the analyses undertaken in the thesis is different in three main ways. First, direct standardisation of rates was performed so that rates reported in this thesis can be compared to future studies. Direct comparison with these previously reported crude rates may have lead to erroneous findings of agreement of leg ulcer rates by failing to account for different population structures that were evaluated between studies(Graham et al. 2003a). Second, attempts were made to quantify the effect of socio-economic and other variables on rates of leg ulcers. Previous studies examining leg ulcer rates had never extended methods beyond stratification. The regression methods used in the thesis have produced estimates which are less prone to bias than earlier findings. Third, the work has also attempted to examine the extent of leg ulcer guideline implementation on nationally representative data whilst also using robust methods such as multilevel analysis to examine the factors that contribute to variations in implementation.

The analyses in this thesis have provided epidemiological results that expanded beyond the initial examination of venous leg ulcer incidence and prevalence in persons aged 65 years of greater using the GPRD as undertaken by Margolis et al. (2002). Additionally, the work conducted in chapters four and five also used regression techniques to statistically analyse the relationship between rates and age, gender and study year, and in the THIN database, Townsend deprivation fifth rank. The use of regression adds extra precision to the results as multiple adjustment of variables on leg ulcer rates was performed. The second difference of the work undertaken in the thesis was that unlike previous studies that have used routinely collected data, the two databases used are subject to checks to ensure that only valid and reliable data is included. The third difference was that the studies examining burden of disease and management conducted in chapters three, four and five were not subject to selection bias as all eligible leg ulcer patients were included in the analyses.

No other studies were located that had compared estimates of disease burden from the GPRD and THIN databases for any clinical conditions. The work undertaken in chapter three of this thesis therefore represents first time evidence of the comparability of these databases for the study of leg ulcer rates. As these results were comparable it also less likely that there would be any bias in the results of patient management. Bias may have been present if there were vast differences in the population profiles of the databases, as patient characteristics may themselves be related to leg ulcer management.

The expansion of this investigation of primary care databases to evaluate patient's management has been documented for many other clinical conditions but no work was found that used these resources specifically for leg ulcer management. The work undertaken in this thesis was shaped by the availability of new sources of data which provided the capacity to investigate the role of socio-economic factors in relation to the burden and management of leg ulceration and the availability of clinical trials data. These data enabled me to apply novel methodological that provided robust evidence of socio-economic relationships with leg ulcer rates, management and outcomes.

Although there have been several studies examining the management of leg ulcers in a variety of clinical settings, none of these studies examined factors that may contribute to variations in care. My work therefore, provides first time evidence of the low rate of reported guideline implementation in general practice and shows there is considerable variation between practitioners in implementing the guideline recommended care for leg ulcer patients. Evidence from other studies suggested that this may also be the case in terms of the care provided by community nurses (Hickie et al. 1998; Clarke-Moloney et al. 2006).

7.3.2. Use of clinical trials data to explore socio-economic contribution to wound healing

It was hypothesised that there would be relationships between socio-economic position and wound healing as there are relationships between acute wound healing and stress and that stress responses may vary by socio-economic position (Steptoe &Marmot 2002; Walburn et al. 2009). There has been only one examination of the relationship between stress and healing of chronic wounds (Cole-King &Harding 2001). There is also evidence to suggest that patients of lower socio-economic position are more likely to develop post-operative wound healing complications, such as MRSA (Bagger et al. 2004).

No previous studies were found that examined socio-economic factors as potential confounders or effect modifiers in randomised controlled trials for evaluation of interventions for persons with leg ulcers. Nor had the generalisability of patient's socio-economic factors in clinical trials been

evaluated. Therefore the work conducted in chapter six therefore provides first time evidence of these relationships in persons with leg ulcers.

7.4 How does this thesis confirm or challenge other research?

An earlier systematic review of leg ulcer prevalence studies undertaken by Graham et al. (2003a) had suggested that higher rates of leg ulcers were found in older patients and women, however these results were based on stratification of rates. The findings of the results of chapters four and five, undertaken using regression analyses, consistently showed that older age and female gender are associated with higher rates of leg ulceration and are less prone to bias than earlier findings. The findings that area level socio-economic measures are associated with higher levels of venous leg ulcer prevalence is supported by earlier evidence showing associations with individual level measures of socio-economic position (Fowkes et al. 2001; Moffatt et al. 2006). The results from this thesis show that there is evidence of socio-economic variations in some aspects of leg ulcer management.

Most leg ulcers encountered in primary care were recorded as being venous in origin with over 90% having this definition. These results are in contrast with previous studies examining the pathophysiology of leg ulcers which have shown that greater numbers of ulcers are due to arterial and mixed venous arterial aetiology (Cornwall et al. 1986; Moffatt et al. 2004; Vowden &Vowden 2009). In contrast to the results from primary care databases obtained in this study, these earlier studies examining the aetiology of leg ulcers were undertaken using standardised assessments and many used device based testing to evaluate leg ulcer circulation. The results of leg ulcer aetiology obtained in the current study may lack the accuracy of these earlier findings resulting in overestimates of venous leg ulcer rates and underestimates of non-venous leg ulcer rates.

Existing studies of leg ulcer management highlight the varied level of implementation of guideline recommendations for care. This was further confirmed in analyses undertaken using the GPRD and the THIN database in chapters four and five. The results obtained in the thesis were obtained from a wide spectrum of practices showed that there was considerable variation in the reported degree of implementation at the practice level. Models of patient management demonstrated that upwards of 29% of all variation was at the practice level.

These findings from chapters four and five resonate with the results of many studies in other disease areas that have found gender and socio-economic associated health inequalities in the provision of care (Hippisley-Cox et al. 2007; Stock et al. 2008). In contrast to findings produced by McLean et al. (2006), the current analyses did not find a greater effect of deprivation when measured at the practice rather than patient level. It was not possible to examine the effect of

practice level deprivation on disease rates as these data were not available for the denominators of rates in the GPRD. In the study conducted by McLean et al. (2006) prevalence rates of cardiovascular disease, examined by deprivation fifth membership were shown to be overestimated when deprivation was measured at the practice level rather than using individual measures. The authors of this study did not utilise any multilevel methods which would have allowed them to quantify the relative contribution of deprivation at both the patient and practice level. It is unknown if similar results may exist for leg ulcer patients as the data did not support this type of analysis at the time this study was conducted.

The work conducted in chapter six confirms the results of research conducted by Franks et al. (1995a) showing that there is no impact of patient's socio-economic position on healing outcomes when provided with high quality standardised care. The hypothesised pathways between socio-economic position, stress and wound healing were not evident from the results of the analysis undertaken using the VenUS I and II trials. There are two possible explanations for this finding. First, the measure of socio-economic position used may not correlate with measures of stress. Second, that other known prognostic factors such as wound size and duration may be of greater importance than stress in the healing of chronic wounds. This work represents the first time these questions have been explored using randomised trial data which has the potential to control for both known and unknown confounders and are less prone to bias than reports based on observational data.

There was no evidence of the socio-economic relationship with adverse events, such as MRSA, that was identified in the earlier work examining these outcomes in surgical wounds undertaken by Bagger et al. (2004). The work undertaken by Bagger et al. (2004) did however have a much a larger sample size (n>1500) and it was acknowledged by Dumville et al. (2009) that the numbers of patients identified with MRSA in VenUS II trial were lower than expected. It may have been that the VenUS II trial was underpowered to examine the relationship between socio-economic position and MRSA should it exist.

7.5 What are the strengths and limitations of the methods used?

Although the strengths of limitations of individual studies have been discussed within each chapter in turn there is a need to provide an overview of key areas which are central to the thesis. These key areas are (i) the strengths and limitations of using of secondary data and (ii) the use of proxy measures (area) measures of socio-economic position.

7.5.1 Secondary data

There are many positive characteristics of using secondary data for the conduct of epidemiological and health services research. First, it allows for the collation of evidence in a timely, cost-effective manner negating the need to set up expensive primary studies such as cohort studies. Given the size of the populations included in these databases there is also the ability to study rare outcomes. Second, there is the potential to produce evidence that is less prone to bias than many earlier leg ulcer studies. There is no selection bias as there is no need for patients to be contacted or consent for a research study. In the majority elderly population that has leg ulcers this may be important as patients may not be able to travel to take part in research, be able to provide informed consent to participate or may have multiple co-morbidities which may impede participation. Non-participation bias is eliminated as all patients with a diagnostic code of leg ulcers can be included in the evaluation using prospectively collected data. Finally, as prospective medical records are used there is no bias introduced through recall error as both patients and practitioners may have forgotten key details of disease duration or management decisions made.

There are two additional benefits that are accorded by use of the GPRD and THIN databases. First, both databases include indicators of quality so that analysis can be restricted to the best quality data that is available and bias minimised. Second, the data contributed to these databases come from practices nationally that are representative to the wider UK population (Hippisley-Cox &Coupland ; GPRD 2010).

Despite these positives, the use of secondary data is not without limitations. Foremost of which is that all results from studies using such data are based on reported rather than actual practice. Whilst the data in both the GPRD and THIN databases are subject to many quality checks, it is inevitable that the data will contain some errors. My results clearly indicate there is some degree of diagnostic misclassification of patient's with a database diagnosis of venous leg ulceration. The data in these databases is from routine patient care rather than for a purpose built research study. This means there will be limited availability and recording of confounding variables that are relevant for all clinical conditions. In the case of the current analyses, I have not been able to control for the effect of size and duration of leg ulcers in any of the examination of leg ulcer burden or management. This is despite knowing that these two variables are key predictors of leg ulcer healing. Leg ulcer size was not available in the database and due to the characteristics of primary care coding duration data will be underestimated for this condition. I have however, been able to control for these two key confounding variables when examining the role of socio-economic factors in healing using data from randomised controlled trials, where baseline adjustment for these confounders was undertaken.

7.5.2 Proxy measures of socio-economic position

The analyses presented in the thesis measured socio-economic position using a proxy measure, the Townsend deprivation index, measured as either a score or fifth rank. Further analysis of management in the GPRD also measured practice level deprivation as a proxy for individual deprivation, but in this instance the IMD England 2000 was used.

Using proxy measures of deprivation in the analyses undertaken in the thesis has had many advantages. The measures used were available for all patients in the database and the two randomised controlled trials allowing comparisons to be made between these populations. As these measures have been widely used in the health literature for some time, it allows other authors the chance to examine the relative contribution of Townsend deprivation fifths to health burden and outcomes for the population with leg ulcers. The Townsend deprivation Index has been shown to be highly correlated with health outcomes. Finally, work undertaken by Krieger (1992) has indicated that using area levels may be an adequate proxy in the absence of individual socio-economic data whilst Adams (2005) finds that they are just as good as individual measures at predicting self reported health. A final advantage of this approach is that it does not require research participants to disclose any potentially sensitive information such as income.

The use of proxy measures may also have some disadvantages. First, there is always the possibility that any results obtained using proxy measures may be subject to ecological fallacy. The ecological fallacy results when inferences are made using data from one unit of measurement (e.g. an area) and construing the results to another unit of measurement (e.g. an individual). An example of this would be an area in which a person resides may be poor but not all individuals living in that area will be poor. A second disadvantage is that reverse causality cannot be ruled out as a potential explanation of the results (e.g. that ill health led to being poor or living in a poor area rather than poverty being the cause of illness).

Despite this caution the results of this thesis suggest that both context and composition will contribute to health inequalities. Ideally the role of individual and area measures would have been evaluated simultaneously and their relative contribution to ill health calculated. This was not conducted however, as no individual measures were available for analysis. The results of previous analyses undertaken by Breeze et al.(2005) and Grundy & Holt (2001) suggest that both individual and area variables explain associations with health independently in the elderly population. It is likely therefore that the examination of socio-economic position undertaken in this study explains only a proportion of the socio-economic variation experienced.

7.6 Research, policy and practice implications of the findings

Routine data

Routinely collected data has the potential to facilitate the timely production of public health and health services research evidence needed by policy and decision makers in the Department of Health and the National Health Service.

Despite the potential of these data it may be that some clinical conditions have characteristics that are better suited to using a routine data approach for the production of this evidence. A recent study evaluating the prevalence of wheeze and asthma in children has demonstrated that reliance on Read codes for the identification of cases will result in underestimates of the prevalence of the condition (Turner et al. 2009). Far greater numbers of patients with asthma were identified when a combined prescription and Read code case identification strategy was implemented. This approach was not possible in the thesis due to the heterogeneous prescribing practices that were evident from the results examining reported leg ulcer patient management in chapters four and five. Whilst it is likely that the prevalence estimates obtained in this study are underestimates it is not thought that incidence would be affected as it appears improbable that there would be a propensity to not record a leg ulcer diagnosis at some point during the patients care. Researchers utilising the GPRD and the THIN databases should be aware that prevalence estimates of chronic conditions will almost certainly be an underestimate due to the way users are instructed to record clinical events.

Furthermore, greater diagnostic accuracy will be obtained where there are strict diagnostic criteria for the identification of a condition. As was observed in the studies conducted in chapters four and five reported usage of device based testing in leg ulcer management was low, irrespective of the database diagnosis of leg ulceration examined. Even so the level of detail available in the electronic records from general practice would be insufficient to enable any external judgements to be made regarding the accuracy or appropriateness of the database diagnosis of leg ulceration given to patients.

Research possibilities of future data collection strategies

Due to changes in data collection and availability further exploration of two key factors not able to be explored in the thesis are now possible. The first change has been the availability of proxy patient level socio-economic data in the GPRD, in addition to practice level deprivation data. The availability of this data will allow the relative contribution of patient and practice level to variations in management to be quantified. The second change in data availability is a national initiative to improve the quality of ethnicity available from primary care. Very little work has been undertaken examining the relationship between ethnicity and leg ulceration. Only two studies were found that had performed any exploration of the issue finding some variations in leg ulcer rates by ethnicity

(Franks et al. 1997; Moffatt et al. 2004). In February 2009, under the guise of the National Health Service Act 2006, there have been amendments to the primary medical services (directed enhanced services) which place a responsibility for collecting ethnicity and language spoken by person seeking care within primary care trusts (Lakhani 2009). Despite being an area that attracts additional funding under the QOF scheme, recent data from 2008/2009 suggested that only 63.8 % of practices achieved QOF points for this domain (The Information Centre 2009).

There are likely to be higher rates of leg ulcers in persons from Black and minority ethnic groups in the future as many risk factors that underlie diseases that cause leg ulceration are increasing in these populations. Studies of childhood obesity continue to show that children from Black and minority ethnic groups are at an increased risk of becoming obese compared to their White British peers (Saxena et al. 2004). There is also evidence to suggest that persons of South Asian ethnicity are at an increased risk of a range of conditions related to obesity, such as the metabolic syndrome and diabetes, that will increase risk of the development of diseases that underlie leg ulceration (Rafnsson &Bhopal 2009).

There are further initiatives in place to improve in data collection which may yield new possibilities for research and provide opportunities to fill the gaps regarding the management of leg ulceration outside of general practice. The implementation of large scale projects such as the National Programme For IT and the use of linked health records have the potential to expand the analysis and overcome many of the limitations (e.g. lack of data from community nursing) and gain a greater understanding of the patient journey between primary, community and secondary care.

A gap that could be filled by primary care to improve the evidence base of care provision would be to record individual socio-economic indicators for all registered patients in the same way as other key demographic data is collected. This data could include indicators that would be easy for patients to report such as educational level and occupation. It is hypothesised that this would improve commissioning and research data and would help primary care providers to ensure that they are monitoring variations in care and health needs of the patients they treat. Many of the recent intervention recommendations made in the Strategic Review of Health Inequalities in England may emphasised the need to ensure that commissioning is based on the local needs of individuals (Marmot 2010).

Implementation

Future work also needs to focus on developing strategies to improve the implementation of evidence based leg ulceration care in primary care. Doppler assessment of leg ulceration is optimal but can take considerable time to perform, with previous estimates of mean time taken of 9

minutes (Deveugele et al. 2002). Data on consultation length is not currently collected by any UK primary care database, although it hyothesised that this may often be lower than the time required to undertake Doppler assessment and warrants further investigation. Further work is required to develop more effective strategies for the implementation of leg ulcer guidelines. This work provides further evidence that if implementation is sub-optimal health inequalities may be further exacerbated.

The documented management of leg ulceration in primary care provides yet more evidence of 'translation gaps' between the production of evidence and its implementation in practice that have been identified by others as major impediments (Glasgow &Emmons 2007; Lynch et al. 2010). Lynch et al.(2010) highlighted the advantages of linked records to both increase the capacity to routinely evaluate the equity and effectiveness of changes in service delivery and to enable explanatory and pragmatic trials to be embedded in population wide information systems. This thesis has demonstrated that it is possible to use linked primary care records for routine evaluation of leg ulcers. However, it was found that it was not possible to use records to evaluate outcomes following leg ulcer management due to the paucity of outcomes data available. In the case of leg ulcer outcomes, particularly healing, confounding by indication would be a real possibility as insufficient data on key baseline prognostic factors such as wound size and duration are not available.

Utilising clinical trials data it has been possible to show that guideline recommended management may have the potential to alleviate the health, gender and age related inequalities observed in results of reported management of venous leg ulcers. Given this evidence the priority for further research should be to ensure that these guideline recommendations for leg ulcer care are implemented more widely and ensuring that populations most at need are adequately targeted.

Marmot (2010) asserted *'that are two major challenges: to improve health for everybody and to reduce inequalities. In Britain we have done well on the first; not on the second'*. The findings of this thesis in relation to leg ulcer epidemiology and care, resonate with these words. Although positively the results of chapter six have shown that despite their being a greater prevalence of leg ulcers in persons living in more deprived areas there was no evidence of worse outcomes when high quality management was provided.

It is therefore concluded that the research priority for the reduction of inequalities in leg ulcer prevalence must be to ensure that the implementation of leg ulcer guidance is increased amongst providers treating the condition. Interventions required to reduce health inequalities in the

incidence of leg ulceration will require cross-departmental policy initiatives to work to reduce health inequalities in the wider determinants of health.

The widespread utilisation of electronic records by health care providers opens up the possibility of undertaking further research programmes to improve the implementation of leg ulcer guidelines in primary care and by other care providers such as district nurses. First, it is proposed that a qualitative research stream undertaken to understand what barriers practitioners face when trying to implement the findings of leg ulcer guidelines and in particular the use of compression bandages. It is not clear whether this non-implementation comes from a lack of provision of this treatment or whether patients are resistant to this form of therapy. Earlier work undertaken by Van Hecke et al (2008) suggests that there is little evidence of strategies to improve patient compliance with compression therapy. Second, it is proposed that research into effective strategies to implement leg ulcer guidance is conducted to ensure that health inequalities in leg ulcers are reduced and that quality improvements in leg ulcer care are achieved. Implementation research involving practitioners that contribute to primary care databases would allow accurate recording of leg ulcer management, however additional data collection strategies would be required to obtain outcomes data.

7.7 Conclusions

A dose response relationship between socio-economic deprivation and rates of incident and prevalent venous leg ulcers and prevalent arterial leg ulcers was observed. Rates were shown to increase by ten percent for each subsequent increase in deprivation fifth membership. Rates of mixed leg ulceration showed no association with deprivation although the numbers of patients with this diagnosis may have been too small to find an association should one exist. These relationships were evident even when adjusted for other risk factors including age, gender and study year.

There is some indication that there may be a degree of error in the diagnostic accuracy in the recording of leg ulcer diagnosis. Frequencies and proportions of persons with venous leg ulcer do not concord with previous leg ulcer aetiology assessments, overestimating the proportion of patients with venous leg ulcers. Despite this there appeared to be no systematic differences in the proportion with different aetiologies of leg ulcers between the GPRD and THIN databases.

Socio-economic deprivation was shown to be associated with the reported choice of initial assessments undertaken in venous leg ulcer patients. Patients living in more deprived areas or those attending practices in more deprived areas of England, were female and of increasing age were found to have lower odds of receiving an assessment of their ankle brachial pressure index. Deprivation was not shown to influence any other aspects of leg ulcer management examined, such as the provision of compression therapy and referrals to other leg ulcer care professionals. With the exception of reported assessment of ABPI which was shown to be increasing over time, there appeared to no change in other aspects of guideline recommended care which had been introduced in 1998.

Deprivation was assessed as a potential confounder or effect modifier with the relationship between healing and adverse events which included infections and MRSA. No association was observed between deprivation and either outcome. The results in this thesis demonstrate that, although higher socio-economic deprivation is related to higher rates of leg ulceration when patients are provided with high quality care there is no evidence that there are detrimental impacts on patient outcomes such as healing.

The external generalisability of the two trials of the largest trials of leg ulceration were examined, and were both found to be representative of the population seeking care for their leg ulcers in primary care. No major discrepancies were observed between any of the patient characteristics captured in the primary care databases and those captured in clinical trials data. These included age, gender and Townsend deprivation

Future research should focus on effective guideline implementation strategies so that health inequalities evident in the development of leg ulcers are diminished. The evidence obtained from this thesis suggests that equal application of guideline based care has the potential to reduce the inequalities observed in leg ulcer development.

8.0 APPENDICES

Appendix A Prevalence studies

Author	Population	Methods	Clinical validation	Definition	Foot Y/N	Age group	Total prevalence	Prevalence by sex	Any other variables examined
O'Brien et al. 2000*	Health district 317,069 Ireland RR: 97-100%	Survey of all professionals, health care facilities, and self-care	Yes 38%	Open sore below the knee	Yes	All	Crude 0.12 Age standardised 0.118	Increase with age Females<Males post 60 years	
Marklund et al. 2000*	Rural area Sweden 4000 RR: 98%	Telephone interviews and postal survey in the community	Yes 99%	Ulcer distal to knee that did not heal within 6 weeks O & H	Yes	≥70 years	8.5◊	Not reported	
Nelzen et al. 1996*	Malmo City and Skaraborg county; Sweden RR: 90%	Random sample; postal survey in community	47%	Open wound below the knee that did not heal within 6 weeks O & H	Yes	All	1.8◊ Open only 0.63 (0.54-0.72)	Not reported	

* Study included in Graham et al. (2003) systematic review

Author	Population	Methods	Clinical validation	Definition	Foot Y/N	Age group	Total prevalence	Prevalence by sex	Any other variables examined
Andersson et al. 1993*	Göteburg, Sweden RR: 89%	Random sample; postal survey in community	77%	Ulcer situated on lower legs or feet caused by altered blood flow	Yes	Unclear	On exam 1.02 (0.7-1.3) Female 0.86 (0.1-1.6) Male 1.27 (-.04-2.9) Healed 2.99 (2.5-3.5)	Increases with age Males<Females post 65 years	
Baker et al. 1994*	Health district 238,000 Perth Australia RR: NR	Survey of professionals, health institutions, and self-referral	93%	Defect in the dermis at site below knee, persistent for 1 month or longer	Not reported	All	Total 1.1	Increases with age Females<Males post 50 years	

* Study included in Graham et al. (2003) systematic review

Author	Population	Methods	Clinical validation	Definition	Foot Y/N	Age group	Total prevalence	Prevalence by sex	Any other variables examined
Nelzen et al. 1991* Nelzen et al. 1994*	Skaraborg county 270,800 Sweden RR: varied from 59% to 100%	Survey of all community nurses, nurses working in GP offices, outpatient departments, long-term care hospitals, and private long term care facilities.	~48%	Open wound below the knee that did not heal or was supposed to heal within a 6 week period after the onset of ulceration	Yes	All	1991 study: 0.305 1994 study: Venous leg ulcers only 0.16 (0.15-0.18)	1991 and 1994 studies. Increases with age Females<Males post 55 years	
Cornwall et al. 1986*	Regional health district 198,900 United Kingdom RR: NR	Survey of all GPs, community and practice nurses, hospital wards, and outpatient departments	67%	Not reported	Excluded	Unclear	0.18	<40 years for both Males and Females 0.38	Ulcer aetiology

* Study included in Graham et al. (2003) systematic review

Author	Population	Methods	Clinical validation	Definition	Foot Y/N	Age group	Total prevalence	Prevalence by sex	Any other variables examined
Coon et al. 1973*	Tecumseh, Michigan, USA Sample size not stated RR: Unclear	Longitudinal study Where patients recruited from not stated	Unclear	Not reported	Excluded	Age ≥10 years	0.2◊	Increases with age Females<Males post 50 years	
Franks et al. 1997*	West London, Health Care trust, United Kingdom RR: NR	Survey of GPs, community and practice nurses, hospital wards, and outpatient departments.	NA	Not reported	Not reported	All	0.12	Increases with age Females<Males all age groups	

* Study included in Graham et al. (2003) systematic review

Author	Population	Methods	Clinical validation	Definition	Foot Y/N	Age group	Total prevalence	Prevalence by sex	Any other variables examined
Ebbeskog et al. 1996*	Stockholm medical area; 241,804 Sweden RR: 87%	Survey of private practitioners, 1 major and 1 minor hospital (including outpatient clinics), 3 geriatric clinics, 8 nursing homes	NA	Not reported	Yes	≥34 years	0.12 (0.08-0.16)	NR	
Lindholm et al. 1992*	Malmo, 232,908; Sweden RR: varied from 67% to 97%	Survey of 54 hospitals wards, 11 primary care centres, 11 geriatric rehabilitation, 37 homes for the elderly, 3 private homes for the elderly, 8 psychogeriatric clinics, 3 group living elderly units, 1 dermatology department	NA	Chronic ulcers below the knee; ulcers below the knee registered as foot ulcers.	Yes	30+	0.12	NR Prevalence increased with age	

Author	Population	Methods	Clinical validation	Definition	Foot Y/N	Age group	Total prevalence	Prevalence by sex	Any other variables examined
Lees & Lambert 1992*	Newcastle health 240,000; UK RR: 84%	Survey of community nurses (70)		Not reported	Not reported	≥45 years	0.19	NR	
Henry 1986*	Ireland RR: Not reported	Random sample; postal survey of community nurses		Open sore on legs that would not heal	Not reported	≥25 years	1.5	Increases with age Females<Males all age groups	
Callam et al. 1985*	Lothian and Forth valley health boards; 1 million; Scotland RR: varied from 94% to 100%	Survey of all GPs, community and occupational nurses, directors of long term care facilities, and hospital outpatient, inpatient, and physiotherapy departments	40.6%	Not reported	Not reported	All	0.148	Increases with age Females<Males from 55 years	
Andersson et al. 1984*	Hospitals and clinics; 434,699 Göteburg, Sweden RR: NA	Review of medical records	Chart audit 100%	Used ICD codes (1968) Open and closed ulcers	Yes	Not reported	0.32 (0.2-4.0)	Not reported	

Author	Population	Methods	Clinical validation	Definition	Foot Y/N	Age group	Total prevalence	Prevalence by sex	Any other variables examined
Barclay et al. 1998*	2 Hospitals; UK RR: 96%	Cross sectional survey of patients ≤45 years, excluding maternity, psychiatric and paediatric patients	89%	Break in skin	Not reported	Not reported	1.97 (1.23-2.70)	Not reported	
Nelzen et al. 1996*	Industrial workers aged 30-65 years; Skovde, Sweden RR: 87%	Postal survey of factory workers	86%	Any wound below the knee that did not heal within a 6 week period	Yes	30-65 years	0.06 1.9◊	Not reported Prevalence increased with age.	
Maffei et al. 1986*	University health centre; Sao Paulo, Brazil RR: NR	Survey completed on each patients by social worker prior to medical consultation	100%	Presence or history of an ulcer associated with signs of CVI and a complaint of delay in healing	Not reported	Not reported	3.6◊	Female 4.1◊ Male 2.5◊	

Author	Population	Methods	Clinical validation	Definition	Foot Y/N	Age group	Total prevalence	Prevalence by sex	Any other variables examined
Dale et al. 1983*	Single group practice; individuals ≥65 years; Scotland RR: 77%	Random postal survey; patients attending the practice.	Unclear	Open sore below the knee that took longer than 6 weeks to heal	Yes	Unclear	0.8 Adult population: 1 <65 years 3.6	Not reported	
Widmer et al. 1977*	Industrial plants; Basil, Switzerland RR: NR	Survey of factory workers	Not reported	Not reported	Not reported	20-70 years	1.3◊	Female 1.4◊ Male 1.1◊	
Dealey et al. 1999*	Acute care hospital; UK RR: 100%	Survey of all inpatient wards/units	NA	Chronic wounds found on foot or leg below the knee that lasted longer than 6 weeks	Yes	Not reported	1.8	Not reported	

Author	Population	Methods	Type of prevalence	Clinical validation	Definition	Foot Y/N	Age group	Total prevalence	Prevalence by sex	Any other variables examined
Walker et al. 2002a RR: Not reported	North and Central Auckland health district, New Zealand RR: not reported	Survey of health professionals practicing within the study area. Self-referral via telephone for patients to contact researchers.	Point prevalence and Period prevalence	Not reported	A leg ulcer was defined as any break in the skin on the lower leg (below the knee) or on the foot, which had been present for more than 6 weeks	Yes	All	Point prevalence 39 per 100000 (95% CI 34-44) Period prevalence (1 year) 79 per 100,000	Point Prevalence Women 35 and Men 39 per 100,000 persons Period prevalence Women 75 and Men 73 per 100,000 per year	
Walker et al. 2002b	North and Central Auckland health district, New Zealand	As above	As above but using capture-recapture methodology.	As above	As above	Yes	All	Point prevalence 248 per 100,000 Period prevalence 530 per 100000 per year.	Period prevalence Women 516 Men 521 per 100,000	

Author	Population	Methods	Type of prevalence	Clinical validation	Definition	Foot Y/N	Age group	Total prevalence	Prevalence by sex	Any other variables examined
Wipke-Tevis et al. 2000	Residents of Long term care facilities in Missouri	Database search of Minimum Data Set (MDS) Venous ulcers only	Point prevalence	NA	Any open lesion, usually in the lower extremities, caused by decreased blood flow from chronic venous insufficiency.	Not reported	All, but likely to be older adults as in long term care facilities	2.5%	Not reported	
Margolis et al. 2002	Patients registered within the GPRD	Database search for venous ulcer code	Annual prevalence (period prevalence)	NA Database diagnosis validated with original records in sample of patients	OXMIS code suggestive of venous ulcer and no OXMIS code in the next three months suggestive of diabetic neuropathic foot ulcer or ulcer of arterial insufficiency	No	≥65 years	1.69% (95% CI 1.65-1.74).	Not reported	

Author	Population	Methods	Type of prevalence	Clinical validation	Definition	Foot Y/N	Age group	Total prevalence	Prevalence by sex	Any other variables examined
Wong et al. 2004	Health district Kowloon, Hong Kong	Review of nursing records	Point prevalence	No	None provided, although pressure ulcers not included	Yes	65-100	128 per 1000 population 0.13%	Not reported	
Moffatt et al. 2004	Health district, Wandsworth, London	Case ascertainment by health professionals	Point prevalence	Yes	An open wound on the leg which had not healed within 4 weeks	No	All	0.45 per 1000 population	0.34 men 0.54 women per 1000 population	Appears that Denominator entire population not adult population which might suggest why rates are so much lower than other studies
Pina et al. 2005	Hospitals, community services, Lisbon, Portugal	Survey of health professionals	Point prevalence	No	An open wound on the leg.	Not reported	All	1.41 (95% CI 1.25-1.59) per 1000 population	1.30 men 1.46 women per 1000 population	

Author	Population	Methods	Type of prevalence	Clinical validation	Definition	Foot Y/N	Age group	Total prevalence	Prevalence by sex	Any other variables examined
Clarke-Moloney et al. 2006	Health district, Mid West Ireland	Survey of public health and community general nurses	Point prevalence	Not standard but if patients had previously had an APBI measured the results were reported.	Not reported	Not reported	All	0.12% all patients 1.2% patients aged 70 years and above.	Not reported	Proportion of ulcers by pathology
Oien et al. 2006	Health district Blekinge, Sweden.	Survey of all community nurses	Point prevalence	No	Hard to heal leg and foot ulcers not defined.	Yes	All	0.15% for 2004 and 2005	Not reported	Proportion of ulcers by pathology
Vowden & Vowden, 2009	Health district, England	Survey of primary care and nursing homes using trained nurses	Point prevalence	Not reported	Not reported	Not reported	All	0.98 per 1,000 population for all leg ulcers	Not reported	Proportion of ulcers by pathology
McDermott-Scales 2009	Health district, Ireland	Survey of primary and secondary care, nursing homes and mental health	Point prevalence	Not reported	Not reported	Not reported	All	2.9%	Not reported	Proportion of ulcers by pathology

Appendix B Incidence studies

Author	Population	Methods	Type of incidence	Clinical validation	Definition	Foot Y/N	Age group	Incidence rate	Incidence by sex	Any other variables examined
Wipke-Tevis et al. 2000	Residents of Long term care facilities in Missouri	Database search of Minimum Data Set (MDS) Venous ulcers only	Cumulative incidence at 90, 180, 270 and 365 days post admission	Yes 38%	Any open lesion, usually in the lower extremities, caused by decreased blood flow from chronic venous insufficiency.	Not reported	All, but likely to older adults as in long term care facilities Mean age 81.4 years (SD=8.8), range 55 to 109 years	90 days 1% 95% CI 0.8, 1.2 180 days 1.3% (1.0-1.7) 270 days 1.8% (1.3-2.4) 365 days 2.2% (1.6-3.0)	Increases with age Females<Males post 60 years	Pathology not examined although authors have assumed underlying CVI to ulceration.

Author	Population	Methods	Type of incidence	Clinical validation	Definition	Foot Y/N	Age group	Incidence rate	Incidence by sex	Any other variables examined
Margolis et al. 2002	Random sample of elderly patients from the GPRD from 1988 to 1996 with six month baseline ulcer free period from registration and no other leg or foot ulcer diagnosis within the proceeding three months.	Database search for patients with venous leg ulcers	Incidence density	Random sample of patients with database diagnosis were validated with patients original clinical records n=100	Wound in the gaiter area of the limb, an area extending from mid calf to 1 inch below the malleolus, in a person who does not have significant arterial insufficiency of the affected limb.	No	65 years and over	With 6 month ulcer free period 1.16 (95% CI 1.11-1.20) per 100 person years	Men Women 0.50 0.63 0.77 0.89 1.17 1.39 1.78 2.07 2.47 1.75 2.83 2.30 All rates per 100 person years of venous leg ulcers.	 65-70 71-75 76-80 81-85 86-90 91-95

Author	Population	Methods	Type of incidence	Clinical validation	Definition	Foot Y/N	Age group	Incidence rate	Incidence by sex	Any other variables examined
Walker et al. 2002a	North and Central Auckland Health Districts, New Zealand	Cross sectional study Health professional notification and self-referral	Annual cumulative incidence Based on data provided by health professionals or self-report	No	Leg ulcers were defined as any break in the skin or lower leg (below the knee) or on the foot, which had been present for more than 6 weeks	Yes	All	32 per 100000 per year (95% CI 27-37 per 100000 per year)	Age adjusted rates Women 33 per 100000 year Men 26 per 100000 per year Rates similar then women generally <men 50 years	Pathology not examined
Walker et al. 2002b	North and Central Auckland Health Districts, New Zealand	Cross sectional study Health professional notification and self-referral	Annual cumulative incidence Based on data provided by health professionals or self-report Capture-Recapture methodology	No	Leg ulcers were defined as any break in the skin or lower leg (below the knee) or on the foot, which had been present for more than 6 weeks	Yes	All	252 per 100,000 per year 95% CI 138-566 per 100,000	Not reported	

Appendix C Rarer ulcer types

Shown below is an overview of these ulcer types and describes their morphology*.

Condition underlying leg ulceration	Most common location	Morphology
Pyoderma gangrenosum	Lower legs but can occur anywhere on skin	Well-defined, raised, purple, serpigunous, undermined border; rapid development of necrosis and ulceration.
Sickle cell anaemia	Medial malleoli; often bilateral	New ulcers are painful, inflammation may arise on an old scar; may be purulent, have poor granulation tissue, and be non healing if <10cm
Rheumatoid arthritis, Felty syndrome	May occur in unusual locations	Smooth, undulating, irregular 'geographic' shape; can be associated with livedo reticularis and palpable pupura
Hydroxyurea	Malleoli	Painful, persistent; fibrous-appearing with atrophic periulcerous skin
Calciphylaxis	Trunk and limb girdle	Painful subcutaneous nodules to non healing extremity ulcers and gangrene
Osteomyelitis	Foot	Several types: non healing superficial ulcer with thickened, sclerosed bone covered partly by a thin layer of epithelium; deep ulcer, where base consists of excavated bone; or multiple sinuses; or multiple sinuses; sclerotic bone changes and periosteal thickening seen by radiography
Squamous cell carcinoma	When mucosal surfaces are excluded, the most common location is the lower extremity	May be hypertrophic or hemorrhagic; irregular borders; lymphadenopathy; often painless; slow progressive growth.
Basal cell carcinoma	8% of basal cell carcinomas arise on the lower extremity	Chronic ulcer refractory to treatment; may appear benign (i.e. healthy granulation tissue, no rolled pearly border or surface telangiectasia).
Necrobiosis lipoidica (diabeticorum)	Anterior lower limb	Oval or irregular reddish brown plaque with central atrophy and translucent telangiectasias.
Thalassemia	Medial malleoli	Chronic, non painful; shallow with irregular shape; surrounding skin may have no erythema or hyperpigmentation.
Scleroderma	Lower limb	Ischemic skin lesions varying from digital pitting scars to wide ulcers.
Prolidase deficiency	Thigh and lower leg	Skin fragility with leg ulceration and characteristic pitting and scarring; telangiectasias, pupura, lymphadema can also be present; histology is non-specific.
Livedo reticularis	Lower legs, feet, ankles	Fishnet-like skin mottling; colour changes from reddish blue to deep blue mottling upon cold

		exposure; can progress to hemorrhagic blisters and punched-out ulcers; can heal with atrophie blanche.
Pupura	Lower legs and feet	Pupura are often preceded by a burning sensation or pain localised to the affected skin areas associated with oedema; often followed by ulcerations after exposure to severe cold leading to scar formation and brownish pigmentation.
Polyarteritis nodosa	Ankle, lower leg	May present with atrophie blanche
Leprosy	Legs and arms	Posttraumatic with secondary infection or erythema necroticans: angular inflamed lesions that slough to leave deep ulcers
Sarcoidosis	Cutaneous involvement in approximately 25% of cases; ulcerative lesions are rare but usually occur on the legs	Small, usually 1-2cm, frequently resolve with systemic corticosteroid therapy.
Livedo vasculitis	Lower extremities	Focal pupura preceding to configurate, stellate, infarctive ulcers covered with dark adherent eschar
Other anemias	Variable	
Erythema induratum of Bazin	Posterior aspect of lower third of calves	Persistent and recurrent nodules that often ulcerate in cold weather; lower calves may plump with erythocyabotic circulation and follicular hyperkeratosis; ulcers are irregular and shallow with bluish tense borders; usually heal spontaneously within several months, leaving atrophic hyperpigmented areas, histologically appears as a tuberculoid granuloma with or without caseation and may involve subcutaneous vessels or fat
Behçet disease	Oral and genital; rarely on the legs	May have features of thrombosis and/or vasculitis
Panniculitis	Variable	Variable
Erythema elevatum diutinum (necrotising vasculitis)	Legs	Large erythematous ulcerated nodules; purpuric eruptions surrounded by warm erythematous skin; depigmentation at site of old healed ulcer; histologically a form of leukocytoclastic vasculitis characterised by an abundant infiltrate of neutrophils
Diphtheria	Legs	Chronic, non healing, slow growing; covered with purulent membrane surrounded by necrotic zone.

*Adapted from Labropoulos et al. 2007

Appendix D Prescriptions and therapies issued within 90 days of incident diagnosis in the GPRD

		Venous	Arterial	Mixed venous arterial
BNF chapter	Any wound therapy	10680/14568 (73.3)	341/479 (71.2)	211/244 (86.5)
Bandages		4325/14568 (29.7)	184/479 (38.4)	100/244 (41.0)
	Light weight conforming bandages	1514	93	36
	Tubular bandages	2716	134	75
	Support bandages	1916	68	50
	Medicated Bandages	557	14	17
	Adhesive dressings	24	2	3
	Skin closure dressings	43	1	0
Compression bandages		2967/14568 (20.4)	103/479 (21.5)	79/244 (32.4)
Dressings		9953/14568 (68.3)	330/479 (68.9)	203/244 (83.2)
	Alginate dressings	7812	264	173
	Foam dressings	2688	123	49
	Hydrogel dressings	1268	81	20
	Hydrocolloid dressings	2302	103	48
	Vapour-permeable films and membranes	603	24	4
	Low adherence dressing and wound contact material	4479	163	80
	Odour absorbent dressings	442	30	10
Stockings		1914/14568 (13.1)	10/479 (2.1)	24/244 (9.8)
Other Therapies		78/14568 (0.5)	8/479 (1.7)	3/244 (1.3)
	Larvae/maggots	6	0	1
	Leg ulcer wrap (magnetic)	4	0	0
	Honey	34	2	1
	Pentoxyfylline	10	2	0
	Debridement	24	4	1
	Vacuum assisted closure	0	0	0

Appendix E Reported referrals in the GPRD, stratified by database diagnosis of leg ulceration.

Referral to:	Venous	Arterial	Mixed
All, n (%)	6287/16920 (37.2)	141/301 (46.8)	40/110 (36.4)
All leg ulcer, n (%)	2,075 (12.2)	68 (22.6)	17 (15.4)
Dermatologist/ dermatological clinic/dermatology special interest GP	667	8	4
Vascular surgeon	304	25	4
Podiatrist/chiropodist/footcare	176	14	2
Specialist leg ulcer or tissue viability services	30	1	0
Pain management/ pain clinic/ pain management nurse	11	2	1
Nursing/ community/practice/district/community matron etc	887	23	10
Intermediate care	867	47	3
Not specified	874	21	14
Casualty/Emergency physician/Trauma/emergency clinic/A&E	287	4	1
Medical/Community medical/ clinical/other physician NOS	193	7	3
Radiotherapy/Radiology/x-ray/Nuclear medicine	176	3	4
Physiotherapist/musculoskeletal clinic	167	5	1
Surgical/general or NOS	169	16	0
Ophthalmology	158	4	4
Orthopaedic	115	4	1
Lab tests	88	1	0
Cardiology/cardiothoracic/cardiology special interest GP	100	5	1
Other diagnostic assessments	75	1	2
ENT	55	3	0
Geriatrics/ care of the elderly physician	65	1	0
Dietician	56	1	1
Genito-urinary/ clinics/ nurses/ vasectomy clinic/ erectile disfunction	40	2	0
Social worker/Social services	45	3	2
Gastroenterology/ upper GI/dyspepsia specialist nurse	41	0	1
Retinal screener	54	1	0
Occupational/art/dance/music therapy	40	1	1
Psychiatric/mental health worker/psychologist/psychiatric nurse	25	2	0
Rheumatology	36	1	0
Obs & Gyn/ related clinics	26	0	0

Haematology	24	3	0
Audiologist	20	0	0
Audiology/ hearing clinic	23	3	0
Psychogeriatrician	27	0	1
Surgical fitter/appliance officer/orthotist	21	2	0
Neurological	19	0	0
Diabetes nurse/ diabetic foot screener	40	0	0
Hospital/day hospital referral	25	1	1
Smoking cessation	20	1	0
Plastics	31	0	0
Counsellor/Bereavement counsellor	10	1	0
Speech therapy	15	0	0
Diabetologist/ diabetes education/screening/clinic	14	1	1
Disablement services	13	0	0
Pathology/Neuropathology	9	0	0
Terminal/Palliative care/Hospice	7	1	0
Urology	8	0	0
Mammography/breast clinic/breast surgeon/breast care nurse	5	1	0
Chest physician/ chest pain clinic	21	1	0
House officer/ hospital registrar	8	0	0
Optician	6	0	0
Endochrinology	3	0	0
Nephrology	9	0	0
Respiratory/ resp nurs	8	0	0
Continence nurse/Incontinence clinic	3	0	0
Dental/Orthodontic clinic	7	0	0
Varicose vein clinic	5	0	0
Colorectal	1	0	0
Falls services/clinics/assessments	0	0	0
Oncology/Cancer/cancer nurses	4	0	0
Colposcopy/Colonoscopy/ Sigmiodoscopy	4	0	0
Lymphoedema care nurse	4	0	0
Stroke services/clinic	3	0	0
Clinical pharmacology/Pharmacist	3	0	0
Maxiofacial	5	0	0
Oral surgery	7	1	0
Alcohol/Drug misuse	1	0	0
Chiropractor	2	0	0
Exercise therapy	1	0	0
Neurophysiologist/physiologist	2	0	0
Phlebotomy	1	0	0
Immunological/allergy	2	0	0
Lipid clinic	0	0	0
Minor injuries/ailments clinic/soft tissue injuries	1	0	0
Neurosurgical	2	0	0
Pulmonary rehabilitation	1	1	0
Warfarin monitoring	2	0	0

Anaesthetist	2	0	1
Cardiac rehabilitation/nursing/ heart failure nurses/ educational/clinics	0	0	0
Cataract/Glaucoma clinic	0	0	0
Community day centre	0	0	0
Eating disorders clinic	1	0	0
Homeopath/Acupuncturist/Complementary therapist	0	0	0
Gynaecology	1	0	0
Memory clinic	0	0	0
Osteopath	0	0	0
Public health	1	0	0
Rehabilitation physician	1	0	0
Thoracic	1	0	0
Renal/Hepatology	1	0	0
Venereology/STI clinics/contact tracing nurse	0	0	0
Weight management programme	1	0	0
Arthroscopy services	0	0	0
Asthma clinic	0	0	0
Burns	0	0	0
Geneticist	0	0	0
GP specific management beta blockers/lipids/aspirin/diuretics/ACE inhibitor	0	0	0
Hand surgeon	0	0	0
Hypertension clinic	0	0	0
Housing department	0	0	0
Intensive care	0	0	0
Learning disability	1	0	0
Occupational health	0	0	0
Orthoptics	1	0	0
Osteoporosis clinic	0	0	0
Oxygen monitoring	0	0	0
Self help for depression/ anxiety/ educational programme	0	0	0
Sexual health	0	0	0
Stoma care/nursing	0	0	0
Telecare	0	0	0
Transplant surgeon	0	0	0
Walk in clinic	1	0	0

Appendix F Prescriptions and therapies issued within 90 days of incident diagnosis in the THIN database

		Venous	Arterial	Mixed venous arterial
BNF chapter	Any wound therapy	10680/14568 (73.3)	341/479 (71.2)	211/244 (86.5)
Bandages		4325/14568 (29.7)	184/479 (38.4)	100/244 (41.0)
	Light weight conforming bandages	1514	93	36
	Tubular bandages	2716	134	75
	Support bandages	1916	68	50
	Medicated Bandages	557	14	17
	Adhesive dressings	24	2	3
	Skin closure dressings	43	1	0
Compression bandages		2967/14568 (20.4)	103/479 (21.5)	79/244 (32.4)
Dressings		9953/14568 (68.3)	330/479 (68.9)	203/244 (83.2)
	Alginate dressings	7812	264	173
	Foam dressings	2688	123	49
	Hydrogel dressings	1268	81	20
	Hydrocolloid dressings	2302	103	48
	Vapour-permeable films and membranes	603	24	4
	Low adherence dressing and wound contact material	4479	163	80
	Odour absorbent dressings	442	30	10
Stockings		1914/14568 (13.1)	10/479 (2.1)	24/244 (9.8)
Other Therapies		78/14568 (0.5)	8/479 (1.7)	3/244 (1.3)
	Larvae/maggots	6	0	1
	Leg ulcer wrap (magnetic)	4	0	0
	Honey	34	2	1
	Pentoxyfylline	10	2	0
	Debridement	24	4	1
	Vacuum assisted closure	0	0	0

Appendix G Referrals reported in the THIN database, stratified by database diagnosis of leg ulceration

Referral to:	Venous	Arterial	Mixed
All, n (%)	4195/14,568 (28.8)	380/479 (79.3)	169/244 (69.2)
All leg ulcer, n (%)	2347/14,568 (16.1)	230/479 (48.0)	97/244 (39.7)
Nursing/ community/practice/district/community matron etc	1248	117	56
Dermatologist/ dermatological clinic/dermatology special interest gp	663	51	26
Vascular surgeon	380	83	24
Podiatrist/chiropodist/footcare	239	55	21
Specialist leg ulcer or tissue viability services	32	2	1
Pain management/ pain clinic/ pain management nurse	20	8	1
Intermediate care	11	3	0
Not specified	896	145	62
Casualty/Emergency physician/Trauma/emergency clinic/A&E	370	47	14
Medical/Community medical/ clinical/other physician NOS	332	64	26
Radiotherapy/Radiology/x-ray/Nuclear medicine	302	41	19
Physiotherapist/musculoskeletal clinic	273	43	9
Surgical/general or NOS	248	58	12
Ophthalmology	206	47	14
Orthopaedic	175	32	14
Lab tests	144	11	7
Cardiology/cardiothoracic/cardiology special interest gp	142	29	9
Other diagnostic assessments	134	24	13
ENT	87	21	6
Geriatrics/ care of the elderly physician	82	11	8
Dietician	72	13	2
Genito-urinary/ clinics/ nurses/ vasectomy clinic/ erectile disfunction	74	13	7
Social worker/Social services	71	11	11
Gastroenterology/ upper GI/dyspepsia specialist nurse	71	13	3
Retinal screener	71	12	8
Occupational therapy/art therapy/dance/music therapy	63	9	6
Psychiatric/mental health worker/psychologist/psychiatric nurse	61	9	1
Rheumatology	50	11	7
Obs & Gyn/ related clinics	47	5	6

Haematology	42	13	2
Audiologist	36	5	1
Audiology/ hearing clinic	39	13	3
Psychogeriatrician	38	6	8
Surgical fitter/appliance officer/orthotist	36	5	5
Neurological	33	2	2
Diabetes nurse/ diabetic foot screener	33	2	2
Hospital/day hospital referral	18	3	3
Smoking cessation	29	5	1
Plastics	26	2	0
Counsellor/Bereavement counsellor	26	2	2
Speech therapy	22	0	0
Diabetologist/ diabetes education/screening/clinic	19	2	2
Disablement services	20	5	4
Pathology/Neuropathology	14	0	0
Terminal/Palliative care/Hospice	20	4	2
Urology	20	2	0
Mammography/breast clinic/breast surgeon/breast care nurse	16	0	0
Chest physician/ chest pain clinic	16	6	3
House officer/ hospital registrar	13	2	0
Optician	13	5	1
Endochrinology	10	1	1
Nephrology	11	1	0
Respiratory/ respiratory nurse	11	1	1
Continence nurse/Incontinence clinic	10	0	0
Dental/Orthodontic clinic	9	0	0
Varicose vein clinic	6	0	0
Colorectal	6	1	1
Falls services/clinics/assessments	6	0	2
Oncology/Cancer/cancer nurses	6	2	1
Colposcopy/Colonoscopy/ Sigmiodoscopy	5	0	0
Lymphoedema care nurse	5	0	0
Stroke services/clinic	5	0	0
Clinical pharmacology/Pharmacist	4	1	0
Maxiofacial	4	0	0
Oral surgery	2	2	0
Alcohol/Drug misuse	3	0	0
Chiropractor	3	0	0
Exercise therapy	3	0	0
Neurophysiologist/physiologist	3	1	0
Phlebotomy	3	1	0
Immunological/allergy	2	0	0
Lipid clinic	1	0	0
Minor injuries/ailments clinic/soft tissue injuries	2	0	0
Neurosurgical	2	1	0
Pulmonary rehabilitation	2	2	0
Warfarin monitoring	2	0	0

Anaesthetist	1	0	0
Cardiac rehabilitation/nursing/ heart failure nurses/ educational/clinics	0	0	1
Cataract/Glaucoma clinic	1	0	0
Community day centre	0	0	1
Eating disorders clinic	1	0	0
Homeopath/Acupuncturist/Complementary therapist	1	1	0
Gynaecology	1	0	0
Memory clinic	1	0	0
Osteopath	1	0	0
Public health	0	0	0
Rehabilitation physician	1	0	0
Thoracic	1	0	0
Renal/Hepatology	1	0	0
Venereology/STI clinics/contact tracing nurse	0	1	0
Weight management programme	1	0	0
Arthroscopy services	0	0	0
Asthma clinic	0	0	0
Burns	0	0	0
Geneticist	0	1	0
GP specific management beta blockers/lipids/aspirin/diuretics/ACE inhibitor	0	0	0
Hand surgeon	0	0	0
Hypertension clinic	0	0	0
Housing department	0	0	0
Intensive care	0	0	0
Learning disability	0	0	0
Occupational health	0	0	0
Orthoptics	0	0	0
Osteoporosis clinic	0	0	0
Oxygen monitoring	0	0	0
Self help for depression/ anxiety/ educational programme	0	0	0
Sexual health	0	0	0
Stoma care/nursing	0	0	0
Telecare	0	0	0
Transplant surgeon	0	0	0
Walk in clinic	0	0	0

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