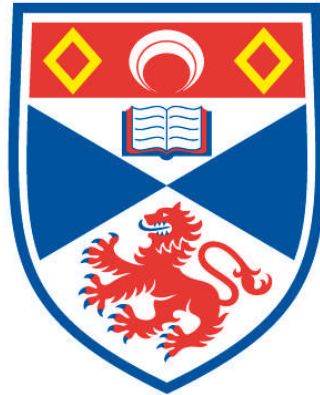


**GEOGRAPHIES OF HEPATITIS C  
EXPLORING THE EXTENT TO WHICH GEOGRAPHIC ACCESSIBILITY  
TO HEALTHCARE INFLUENCES OUTCOMES AMONGST INDIVIDUALS  
INFECTED WITH HEPATITIS C IN NHS TAYSIDE, SCOTLAND**

**Thomas Astell-Burt**

**A Thesis Submitted for the Degree of PhD  
at the  
University of St Andrews**



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# **Geographies of Hepatitis C**

**Exploring the extent to which geographic accessibility to healthcare influences outcomes amongst individuals infected with Hepatitis C in NHS Tayside, Scotland**

**Thomas Astell-Burt BA (Hons), MSc**

**A thesis submitted for the degree of Doctor of Philosophy with the School of  
Geography and Geosciences, University of St Andrews**

**68,000 words**

**October 2009**

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# IV. Abstract

Millions of people are infected with the Hepatitis C Virus (HCV) worldwide. In the UK, many individuals continue to live with undiagnosed HCV infection and are increasingly at risk of developing life-threatening cirrhosis and liver cancer. Of those that are diagnosed, only some are referred to an HCV specialist centre where vital treatment could cure their infection. Of those that are referred, only a proportion have actually attended and stayed in follow-up with a specialist centre. Geographic access to healthcare may be an important factor in these trends, but has so far received little attention in the context of HCV.

This thesis examines the influence of geographic access to primary and specialist healthcare on HCV detection, trends of referral, chances of specialist centre utilisation and the odds of staying in follow-up. It also explores association between geographic access and the type of location in which diagnoses were made with the risk of mortality from liver-related causes. HCV detection was lower amongst those with poorer geographic access to primary healthcare, but further analyses suggest this trend is due to selection, not causation. Individuals with the furthest to travel were less likely to be referred to an HCV specialist centre, compared to those who lived closer. Travel-time was not a significant predictor of utilisation of HCV specialist centres, but with patients in more remote areas less likely to be referred, it is probable that the utilisation result is biased due to selection. Liver-related mortality was higher for patients diagnosed in hospitals, but the risk of death was not associated with a lack of geographic access to healthcare.

# 1. Introduction

“If your thinking is fixed on time to the exclusion of space and society, you will never illuminate anything of the slightest use. So the question arises: why are the spatial dimensions of the epidemic, the geography of this terrible plague, totally ignored?”

(Gould 1993) (p.166)

The plague to which Gould refers was HIV/AIDS. Observing trends in research a decade after the first discovery of HIV/AIDS, with the many studies projecting future burdens of disease, rates of mortality, economic costs and so forth, Gould argued that the ‘where’ questions were being neglected for the ‘when’ and the ‘how much’. 16 years later and researchers with interests in geography have made up significant ground in this regard (see for example (Barnett and Blaikie 1992; Craddock 2000; Kearns 1996; Kesby, Fenton, Boyle, and Power 2003; Setel 2000; Wilton 1996)). Geographies of HIV/AIDS are, in the very least, being explored and written about from all over the world.

Four years prior to Gould’s book, however, a new virus was discovered (Choo, Kuo, Weiner, Overby, Bradley, and Houghton 1989). What was only known in the preceding

years as non-A-non-B hepatitis became referred to as the hepatitis c virus (HCV). In some ways, it is useful to compare HCV with HIV to gain a quick understanding. Like HIV:

- *HCV is a blood-borne virus, sharing some transmission routes (Bellentani, Miglioli, Bedogni, Croce, and Tiribelli 2005);*
- *HCV is largely symptomless during the early years of infection (Alberti, Chemello, and Benvegna 1999);*
- *persons infected with HCV are highly stigmatised (Hopwood and Treloar 2003; Paterson, Backmund, Hirsch, and Yim 2007);*
- *HCV is a worldwide health problem causing high rates of morbidity and mortality (Perz and Alter 2006; Perz, Armstrong, Farrington, Hutin, and Bell 2006);*
- *there is no HCV vaccine (Martin and Inchauspé 2006);*
- *projections of HCV prevalence and the potential burden of liver disease have dominated non-clinical academic research (Alter, Kruszon-Moran, Nainan, McQuillan, Gao, Moyer, Kaslow, and Margolis 1999; Armstrong, Alter, McQuillan, and Margolis 2000; Hutchinson, Bird, and Goldberg 2005).*

There are also important differences. Studies have estimated that three to four times as many individuals are infected with HCV than HIV globally, and we also know that HCV is ten times more infective than HIV (Alter 2006; Shepard, Finelli, and Alter 2005). Moreover, unlike for HIV, HCV can now be practically eradicated by effective treatment in patients diagnosed at an early to moderate stage of infection (Bhopale and Nanda 2005; Dillon 2004; Dusheiko, Barnes, Webster, and Whalley 2000).

However, most infections are not eradicated, or treated at all (Edlin 2004; The Scottish Government 2008). Most individuals with HCV remain undiagnosed, oblivious to the infection and unaware that they might be passing it on (Hutchinson, Roy, Wadd, Bird, Taylor, Anderson, Shaw, Codere, and Goldberg 2006). Unchecked HCV infection can have a large impact on quality of life (Buti, Wong, Casado, and Esteban 2006; Foster, Goldin, and Thomas 1998; Golden, O'Dwyer, and Conroy 2005) and can cause liver cirrhosis, liver cancer and end-stage liver failure (Bosetti, Levi, Lucchini, Zatonski, Negri, and La Vecchia 2007; El-Serag and Mason 2000; Leon and McCambridge 2006), after which the aforementioned treatment is less likely to be successful and the only viable alternatives become a finite number of organ transplants and palliative care (Alter 2007; El-Serag and Mason 1999; Ryder 2007; Ryder and Beckingham 2001b). For many who remain undiagnosed, this is a possible future scenario, with great human and financial cost for wider society (The Hepatitis C Trust and The University of Southampton 2005).

But clearly, the availability of such treatment means that such a scenario need not occur. So, the questions arise: Why do so many individuals with HCV infection remain undetected? And amongst those individuals that have been diagnosed, why is the treatment rate so low?

Research needs to identify potentially modifiable factors which place some people with HCV infection at greater risk of going undetected and untreated. A couple of recent studies in France have suggested that a lack of geographic access to healthcare could be one such risk factor. Indeed, many other academics over the last 30 years have studied influences of geographic access on the detection and utilisation of specialist healthcare pertaining to different types of cancer and other health problems (Bentham and Haynes 1985; Boyle, Kudlac, and Williams 1996a; Fortney, Booth, Blow, Bunn, and Cook 1995; Fortney, Rost, Zhang, and Warren 1999; Haynes and Bentham 1982; Haynes, Pearce, and Barnett 2008; Jones, Haynes, Sauerzapf, Crawford, Zhao, and Forman 2008a; Jones, Haynes, Sauerzapf, Crawford, Zhao, and Forman 2008b; Nattinger, Gottlieb, Veum, Yahnke, and Goodwin 1992; Nattinger, Kneusel, Hoffmann, and Gilligan 2001). Intuition and these findings would suggest that a lack of geographic access to healthcare may also have similarly detrimental influences upon HCV detection rates and the uptake of specialist health services. And yet, sadly, into the twentieth anniversary year of Choo and colleagues report, virtually no similar geographical research has been focused upon the plight of individuals with HCV infection. Gould's question seems more apt than ever:

“why are the spatial dimensions of the epidemic, the geography of this terrible plague, totally ignored?”

The rest of this thesis is dedicated towards formulating an understanding of the HCV epidemic using a geographical lens. First, in a case of problem definition towards developing potential avenues for research, important biological and clinical elements of HCV infection are outlined and then made sense of with respect to social processes and patterns. Second, what we already know of the geographies of HCV is extrapolated and gaps are shaped into feasible research questions. The extent to which geographical accessibility influences health outcomes and could be having detrimental effects on individuals with HCV is explored in detail, followed by analytical chapters, hypothesis testing, and discussion of what the thesis achieved, and what work might still need to be done.

## **2. Epidemiology of Hepatitis C**

### **2.1 Background**

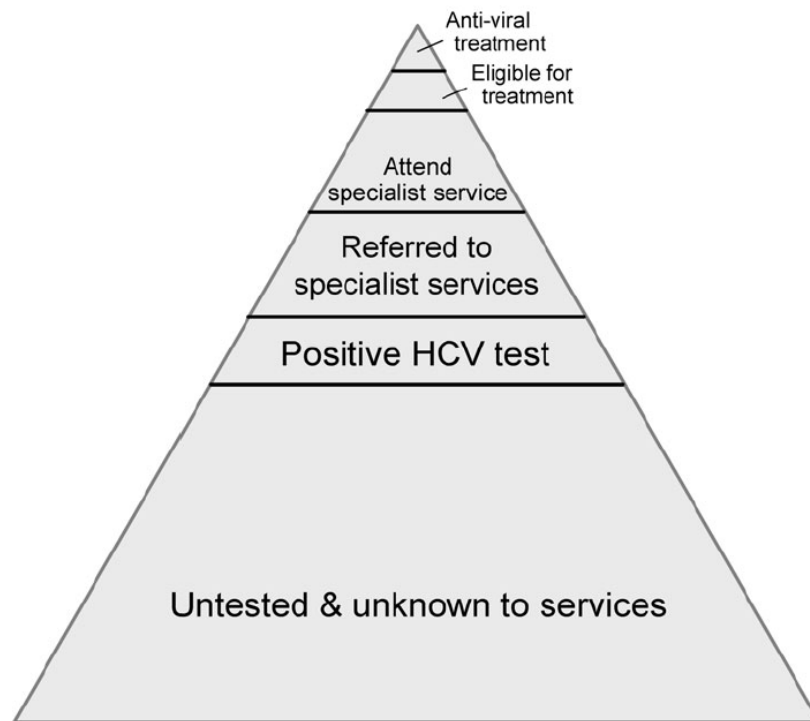
The hepatitis C Virus (HCV) is a blood-borne virus that causes liver disease. Since the discovery in 1989 (Choo et al. 1989), HCV infection has increasingly been recognised as a major worldwide health problem with high morbidity and mortality (Bellentani, Miglioli, Masutti, Saccoccio, and Tiribelli 2000; Khaja, Madhavi, Thippavazzula, Nafeesa, Habib, Habibullah, and Guntaka 2006; La Vecchia, Lucchini, Franceschi, Negri, and Levi 2000; Lavanchy 1999; Monica, Lirussi, Pregun, Vasile, Fabris, and Okolicsanyi 2006). The growing literature on HCV suggests that the number of people infected worldwide is approximately 170 million (Fukushima, Tanaka, Ohfuji, Habu, Tamori, Kawada, Sakaguchi, Takeda, Nishiguchi, Seki, Shiomi, and Hirota 2006; Gerner, Wirth, Wintermeyer, Walz, and Jenke 2006; Hutchinson et al. 2006; Leao, Teo, and Porter 2006; Mohsen and Group 2001), although there are other sources quoting differently.

For instance, Shepard and colleagues report approximately 123 million infected (Shepard, Finelli, and Alter 2005). In a more recent thesis, Alter (Alter 2007) states an increased estimate at 130 million. By comparison, Huang and colleagues report an increased estimate at 180 million infected people (Huang, Murray, and Secrist 2006). Ryder and Beckingham have even suggested estimates of up to 300 million people that may be infected with chronic HCV infection worldwide (Ryder and Beckingham 2001b). Such is the range of prevalence estimates presented is just a glimpse of the:



*“the complexity and uncertainty related to the geographic distribution of HCV infection and chronic hepatitis C, [the] determination of its associated risk factors, and [the] evaluation of cofactors that accelerate its progression, [which] underscore the difficulties in global prevention and control of HCV”*

(Shepard, Finelli, and Alter 2005)(pp.558).



**Figure 7.1: The disease iceberg for hepatitis C (Source: (Parkes, Roderick, Bennett-Lloyd, and Rosenberg 2006))**

Shepard and colleagues statement could also very well apply to smaller scale geographies within national boundaries. Within the UK (Figure 7.1), where it is believed that 466,000 people are infected but only one in seven (approximately 67,000) has been positively identified (The Hepatitis C Trust and The University of Southampton 2005). The seriousness of this apparent failure to diagnose the remaining 86% becomes

apparent when considering that at least 60-80% of HCV infections proceed to chronic HCV (Mohsen and Group 2001) suggest up to 90%) and 20-30% will develop stages of fibrosis after 20 years or more (Haushofer, Kopty, Hauer, Brunner, and Halbmayer 2001; The Hepatitis C Trust and The University of Southampton 2005). In its final stage, fibrosis turns to cirrhosis and HCV becomes lethal, causing hepatocellular carcinoma (cancer of the liver, HCC hereafter) and end-stage liver failure (Fraenkel, McGraw, Wongcharatrawee, and Garcia-Tsao 2006; Massard, Ratziu, Thabut, Moussalli, Lebray, Benhamou, and Poynard 2006; Mondelli, Cerino, and Cividini 2005).

It is anticipated that HCV will play a key role in the future spread of HCC because there is no effective vaccine presently available (Fukushima et al. 2006; Hutchinson et al. 2006), despite a boom in vaccine research over the last 3-4 years (Martin and Inchauspé 2006). To this end, (Golden, O'Dwyer, and Conroy 2005)(pp.431) state:

*“Hepatitis C is now the leading cause of end-stage liver failure and the leading indication for liver transplant in the developed world”*

(see also (Gerner et al. 2006; Perz and Alter 2006; Perz et al. 2006)). To put this back into context, the UK has only seven liver transplantation units, performing 600-700 transplantations a year and with around 200 patients waiting for a liver transplant at any one time (Prasad and Lodge 2001). In a recent report, “The UK vs. Europe – Losing the Fight Against Hepatitis C”, (The Hepatitis C Trust and The University of Southampton 2005) predict a 500% increase in the future demand for liver transplants in the UK and a

financial cost of £8 billion to the NHS. Furthermore, there is mounting evidence that recurrent HCV post-transplant is becoming an increasing problem (Lake 2006; Forman et al, 2002; Berenguer et al, 2000). The enormous health and economic burden presented by HCV is increasingly being recognised in the literature (Dore, Law, MacDonald, and Kaldor 2003; Hutchinson, Bird, and Goldberg 2005; Law, Dore, Bath, Thompson, Crofts, Dolan, Giles, Gow, Kaldor, Loveday, Powell, Spencer, and Wodak 2003; Pybus, Cochrane, Holmes, and Simmonds 2005; Wong 2000).

Despite this bleak outlook, chronic hepatitis C is in fact treatable with National Institute for Health and Clinical Excellence (N.I.C.E.) approved combination drug therapy, with recent studies suggesting between 40-80% of those with moderate to severe diagnoses could be cured (Alberti, Clumeck, Collins, Gerlich, Lundgren, Palu, Reiss, Thiebaut, Weiland, Yazdanpanah, and Zeuzem 2005; Bhopale and Nanda 2005; Everson 2005; Ryder and Beckingham 2001b). (Broers, Helbling, Francois, Schmid, Chuard, Hadengue, and Negro 2005) present evidence from numerous sources demonstrating that the treatment of acute hepatitis C has an even higher success rate at between 80-100% (thus preventing the development of chronic hepatitis C and avoiding more expensive and less tolerated combination therapy).

Yet, it has been reported that only 1-2% of the people who have been successfully diagnosed are treated with these drugs (Loftis, Matthews, and Hauser 2006; The Hepatitis C Trust and The University of Southampton 2005). Many of the non-

geographical reasons for this extremely low treatment rate (mainly focusing on IDU risk behaviour and mental health) have been investigated by numerous authors (Broers et al. 2005; Davis, Rhodes, and Martin 2004; Davis and Rhodes 2004; Edlin 2004; Sylvestre, Litwin, Clements, and Gourevitch 2005; Walley, White, Kushel, Song, and Tulsky 2005). However, the potential influences of geography, particularly geographic access to healthcare, on detection and specialist centre utilisation rates have drawn less attention.

## **2.2 The Liver & HCV**

Holding approximately 13% of the total blood supply at any given moment and performing over 500 estimated functions, the liver (Figure 7.2 and 7.3) is an essential organ in the human body (The British Liver Trust 2009). Some of the most important functions performed by the liver are the regulating, synthesising, storing and secreting of many important proteins and nutrients in the body. The liver is responsible for purifying, transforming, and clearing toxic or unneeded substances (Hopwood and Treloar 2003). The liver can become damaged as a result of inflammation, broadly referred to as 'hepatitis'. Hepatitis can be caused by viral, bacterial, and fungal infections. Exposures to toxins such as alcohol and other drugs or chemical poisons are also significant causes.

Figure 7.2

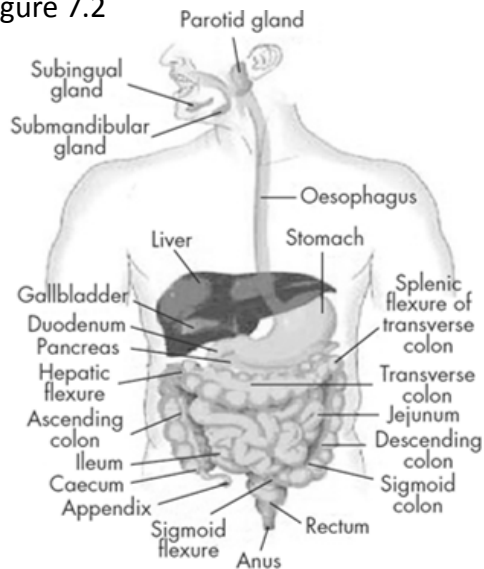


Figure 7.3

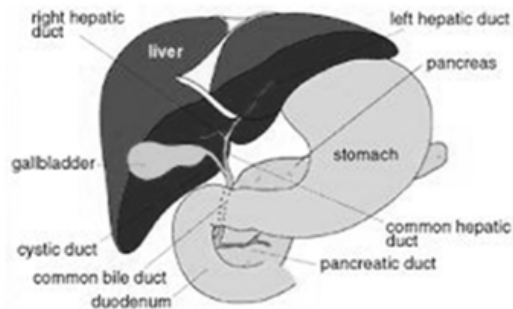
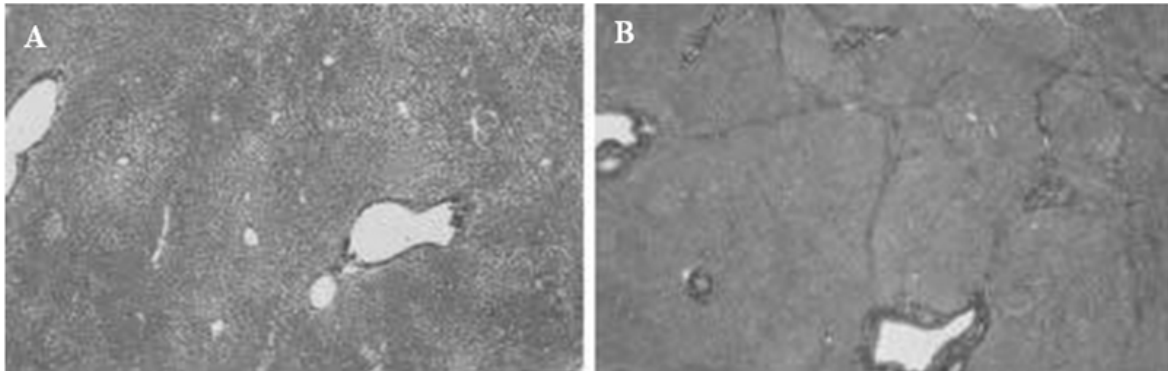


Figure 7.2 (left): The digestive system (Source:(Williams, Roberts, Ali, Cheung, Cohen, Demery, Edwards, Greer, Hellier, and Hutchings 2007))

Figure 7.3 (right): The biliary system (Source: <http://www.britishlivertrust.org.uk/content/liver/about.asp>)

The most commonly reported cause of hepatitis is viral (referred to as ‘viral hepatitis’), of which there are five types: A, B, C, D, or E (Ryder and Beckingham 2001a; Ryder and Beckingham 2001b). Prior to its discovery in 1989, HCV was referred to within the medical literature as ‘non-A non-B hepatitis’ (Hepworth and Krug 1999). Post 1989, a plethora of medical research into HCV has revealed it to be a highly infectious blood-borne virus consisting of six major genotypes and multiple subtypes. The genotype is a very important predictor of the projected response of a patient to anti-HCV therapy and its determination is currently used to specify types of treatment (the genotype’s significance is explored later section in this review). Upon infection, HCV has two phases of development: 1) acute; and 2) chronic.

The term acute is a reference to the ~6-month period of time after the initial infection where it is possible for the body to fight off the disease naturally (of which 25-30% of people infected with HCV successfully do so – The Hepatitis C Trust, 2005). HCV is commonly asymptomatic, which creates problems for early diagnosis (Bellentani et al. 2000; Mondelli, Cerino, and Cividini 2005; Shepard, Finelli, and Alter 2005). It is very common for infection to progress undiagnosed from the acute to the chronic stage unless the immune system can fight it off (Mondelli, Cerino, and Cividini 2005). In layman terms, this means HCV has beaten the natural immune system and continues to develop towards chronic liver diseases (cirrhosis, HCC, and end-stage liver failure) that cause most of the morbidity associated with HCV. It is this asymptomatic nature that has led many to label HCV as another silent epidemic; the silent killer; and the benign virus (Bellentani et al. 2000; Mondelli, Cerino, and Cividini 2005; Mukherjee 2005; Spiess 2001).



**Figure 7.4: A) A normal liver; B) A liver suffering fibrosis (Source: <http://www.britishlivertrust.org.uk/content/liver/about.asp>)**

The chronic phase is characterised by an extended period of development over time leading to cirrhosis of the liver. The spontaneous clearance of HCV is an extremely rare event (Potthoff, Sarhaddar, Wiegand, Lichtinghagen, Sarrazin, Ciner, Hadem, Trautwein,

Manns, and Wedemeyer 2005). The symptoms commonly associated with HCV include tiredness and nausea (Gifford, O'Brien, Bammer, Banwell, and Stoove 2003). The processes borne by the liver during HCV are referred to as fibrosis (Figure 7.4): "the deleterious but variable consequence of chronic inflammation" (Massard et al. 2006), which on average develops over a period of around 20-30 years, albeit with a high degree of variability (Ryder and Beckingham 2001b). It has been reasoned by (Massard et al. 2006) (pp.S19, also see (Poynard, Bedossa, and Opolon 1997; Sobesky, Mathurin, Charlotte, Moussalli, Olivi, Vidaud, Ratzu, Opolon, and Poynard 1999)) that estimating the stage and rate of fibrosis progression is an important proxy for evaluating an individual patient's vulnerability to developing cirrhosis, HCC and liver failure and response to treatment. Recent developments indicate this surveillance may be possible soon (Aguirre, Behling, Alpert, Hassanein, and Sirlin 2006; Blanc, Bioulac-Sage, Balabaud, and Desmouliere 2005; Chung 2006).

After approximately 20 years of active infection, epidemiologic surveys suggest this is the average time that fibrosis progresses to compensated cirrhosis (hardening of liver tissue, preventing the filtering of blood) (Kiyosawa, Sodeyama, Tanaka, Gibo, Yoshizawa, Nakano, Furuta, Akahane, Nishioka, and Purcell 1990; Kiyosawa, Umemura, Ichijo, Matsumoto, Yoshizawa, Gad, and Tanaka 2004; Tong, El-Farra, Reikes, and Co 1995). However, the "rate of fibrosis progression per year and of a mean expected time to cirrhosis does not indicate that the progression to cirrhosis is universal and inevitable" (Poynard, Bedossa, and Opolon 1997).

According to (Everson 2005), the term compensation refers to “patients with biopsy-proven cirrhosis, but who lack significant biochemical deterioration and have not experienced clinical complications.” In other words, the liver continues to function despite extensive scarring. However, patients are at risk of clinical deterioration (decompensation) and advanced liver failure. The symptoms that indicate decompensation include (1) portal hypertension (“when blood cannot properly flow into the liver and causes bleeding from distended veins in the oesophagus and the build up of abdominal fluid”) and (2) hepatic encephalopathy (if blood is forced to bypass the liver it is not filtered for poisons and toxins and there is risk of serious mental confusion leading to coma). Patients at this stage of cirrhosis development are reported to have a five-year survival of 50% (Everson 2005; Fattovich, Giustina, Degos, Tremolada, Diodati, Almasio, Nevens, Solinas, Mura, and Brouwer 1997).

The main factors associated with the progression of fibrosis, and thus an increased risk of progressive liver disease such as HCC, are:

1) **Age greater than forty years old** - the estimated probability of progression per year for men aged 61-70 years is 300-times greater than that for men aged 21-40 years (Deuffic-Burban, Poynard, and Valleron 2002; Poynard, Ratzu, Charlotte, Goodman, McHutchison, and Albrecht 2001; Ryder and Beckingham 2001b);

2) **High alcohol consumption** (toxic levels) (Massard et al. 2006; Poynard, Bedossa, and Opolon 1997; Ryder and Beckingham 2001b; Shepard, Finelli, and Alter 2005). The



influences of alcohol on HCV progression are a contemporary debate within the literature. For instance, (Buti, Wong, Casado, and Esteban 2006) report that in the setting of chronic HCV infection, alcohol ingestion has an additional effect of diminishing immune clearance and increasing viral burden to hasten the onset of cirrhosis and HCC. On the other hand, (Fukushima et al. 2006) found that although high levels of alcohol consumption do influence the development of fibrosis in certain individuals, there is no significant relationship between alcohol consumption and the development of HCC;

3) **Male gender** - males have 10-times more rapid progression to cirrhosis than females, regardless of age (Deuffic-Burban, Poynard, and Valleron 2002; Ryder and Beckingham 2001b);

4) **HIV co-infection** - several studies indicate that patients co-infected with HCV and HIV (and not treated) develop fibrosis levels at a much faster rate than mono-infected patients or patients with other liver diseases, even after taking into account age, gender and alcohol consumption (Pol, Fontaine, Carnot, Zylberberg, Berthelot, Brechot, and Nalpas 1998; Poynard et al. 2001; Poynard, Yuen, Ratzin, and Lai 2003; Soriano 2006). Furthermore, “persons with HCV-HIV co-infection are three times more likely to develop cirrhosis or advanced liver disease [such as HCC] than patients infected with HCV only” (Graham, Baden, Yu, Mrus, Carnie, Heeren, and Koziel 2001; Thimme, Spangenberg, and Blum 2005);

5) **Genotype 1b** – is significantly related to the relative risk of having cirrhosis and/or HCC (Bellentani et al. 2000; Lee, Lu, Hung, Tung, Wang, Tung, Chen, Hu, Changchien, and Chen 2006);

6) **Other conditions** – patients suffering from conditions such as steatosis, type 2 diabetes or obesity as well as HCV have been found to have increased rates of fibrosis (Caldwell, Crespo, Kang, and Al-Osaimi 2004; Massard et al. 2006; Shepard, Finelli, and Alter 2005). There is also recent evidence to suggest that HCV can induce insulin resistance, which means HCV infection can be viewed not only as a liver disease but also a metabolic disease that can lead to the development of type 2 diabetes (Koike 2005).

Increasingly effective treatments are available. The National Institute for Clinical Excellence (NICE) recommends combination therapy of Pegylated Interferon alfa (PEG-IFN) and ribavirin for HCV. The duration of this treatment is based upon the diagnosis of a particular genotype. In general, treatment involves a self-subcutaneous injection of PEG-IFN once a week in combination with 1000mg of ribavirin (patients > 75kg 1200mg) orally per day. In the case of genotypes 2 and 3, 6-months therapy with PEG-IFN and 800mg ribavirin is sufficient (Bhopale and Nanda 2005). The topic of treatment regimens will be discussed in detail further into this chapter.

## 2.3 Worldwide HCV prevalence

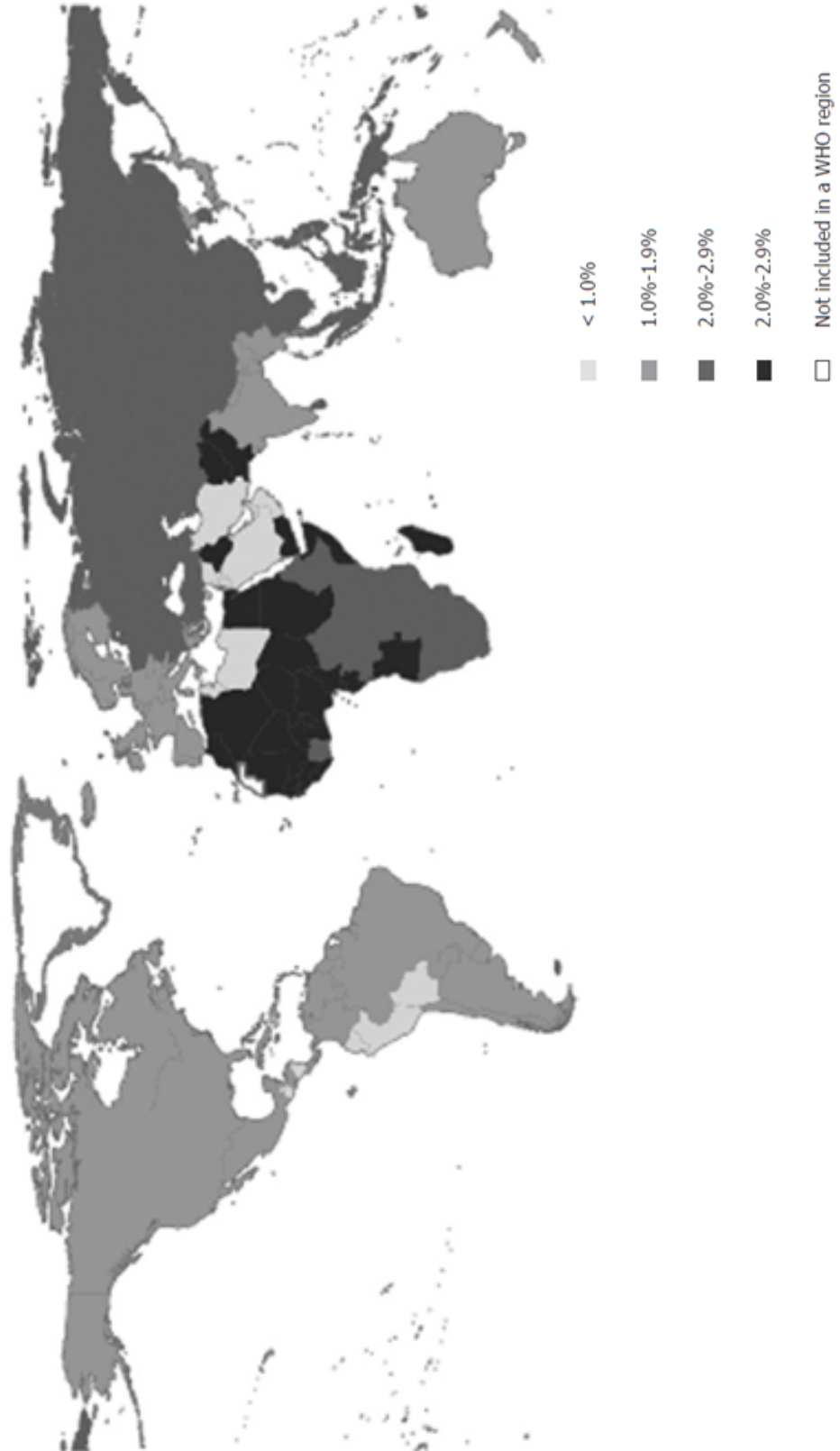


Figure 7.5: Estimated HCV prevalence by region: (Source: (Alter 2007))

HCV is a global pandemic. As noted, it is probable that between 130 to 170 million people have HCV. It is also suggested that 3 to 4 million persons are newly infected each year (The World Health Organisation 2009). With no vaccine currently available, HCV will continue to grow as one of the main causes of cirrhosis and primary liver cancer, which according to WHO estimates in 2002, caused 783,000 and 619,000 deaths, respectively. Taken together, these conditions represented approximately one of every forty deaths (2.5%) worldwide (Bellentani et al. 2000; Perz and Alter 2006; Perz et al. 2006). However, there is a large degree of geographical variance in HCV prevalence (Figure 7.5). (Shepard, Finelli, and Alter 2005) report the highest global prevalence rate, albeit at a rather crude scale, is in the Western Pacific (including China and Japan, 62.2 million). The next highest prevalence rates are in South-East Asia (including India and Indonesia, 32.3 million), Africa (31.9 million), and in the East Mediterranean (21.3 million). Regions of lower prevalence are primarily the Americas (13.1 million), and Europe (8.9 million). Although these figures are highly aggregated, it is clear that HCV presents a greater problem for some parts of the world than others.

(Alter 2006) suggests a scale that the endemicity of HCV infection can be categorised at a regional/country level: high (prevalence  $\geq$  3%); moderate (prevalence 2 -2.9%), low (prevalence 1.0-1.9%), and very low (prevalence  $<$  1.0%). Northern Africa is reported to have the highest prevalence, with Egypt by far the worst reported at between 9% and over 20% of an estimated 73 million population (Ramia and Eid-Fares 2006; Shepard, Finelli, and Alter 2005; Strauss, Rindskopf, Astone-Twerell, Des Jarlais, and Hagan 2006).

There is significant variation in Eastern Europe, ranging from 0.7-4.9% (Bellentani et al. 2000; Kowala-Piaskowska, Figlerowicz, Mozer-Lisewska, Mazur-Melewska, Pawelek, and Sluzewski 2004) and moderate prevalence in most of Asia (Khaja et al. 2006; Leao, Teo, and Porter 2006). Low prevalence rates are reported in Western Europe, North and South America (Alter 1999; Alter 2007; Armstrong, Wasley, Simard, McQuillan, Kuhnert, and Alter 2006; Edlin 2004; Huang, Murray, and Secrist 2006; Macalino, Vlahov, Sanford-Colby, Patel, Sabin, Salas, and Rich 2004; Rocca, Yawn, Wollan, and Kim 2004; Zarife, Silva, Silva, Lopes, Barreto, Teixeira, Dourado, and Reis 2006), and Australia (Dore, Law, MacDonald, and Kaldor 2003; Stoové, Gifford, and Dore 2005), whilst the very lowest prevalence are reported from Northern Europe and the UK (Alter 2006; Alter 2007; Shepard, Finelli, and Alter 2005).

## **2.4 Morbidity and mortality**

The hepatitis C virus (HCV) is a significant cause of HCC and cirrhosis (Giacosa and Hill 1996; Ince and Wands 1999; La Vecchia et al. 2000; Perz and Alter 2006; Perz et al. 2006). The prevalence of HCV in many countries is in some ways a glimpse of the coming wave of HCV-related morbidity and mortality, which is already beginning to manifest itself through the increasing rates of cirrhosis and HCC (see Figures 7.6-7.8) (Perz and Alter 2006; Perz et al. 2006; Shepard, Finelli, and Alter 2005). In the UK

(especially Scotland), France, Japan and the USA, trends in chronic liver disease-related mortality have significantly increased over recent decades (Bosetti et al. 2007; De Vos Irvine, Goldberg, Hole, and McMenamin 1998; Deuffic, Poynard, Buffat, and Valleron 1998; El-Serag and Mason 1999; Hiramatsu, Oze, Tsuda, Kurashige, Koga, Toyama, Yasumaru, Kanto, Takehara, and Kasahara 2006; La Vecchia et al. 2000; Leon and McCambridge 2006; Leyland, Dundas, McLoone, and Boddy 2007; Okuda 1987; Taylor-Robinson, Foster, Arora, Hargreaves, and Thomas 1997). Worldwide, hepatocellular carcinoma (HCC) accounts for between 70-90% of primary liver cancers (Figure 2.8), with over half a million people being detected annually (Bosch, Ribes, Díaz, and Cléries 2004; Parkin, Bray, Ferlay, and Pisani 2001; Yu and Yuan 2004) and a 5-year survival of approximately 5% in most countries (El-Serag and Mason 2000).

Figures 7.6-7.8: HCV-related mortality (Source; the 'Worldmapper') - Territories are sized in proportion to the absolute number of people who died in one year from:

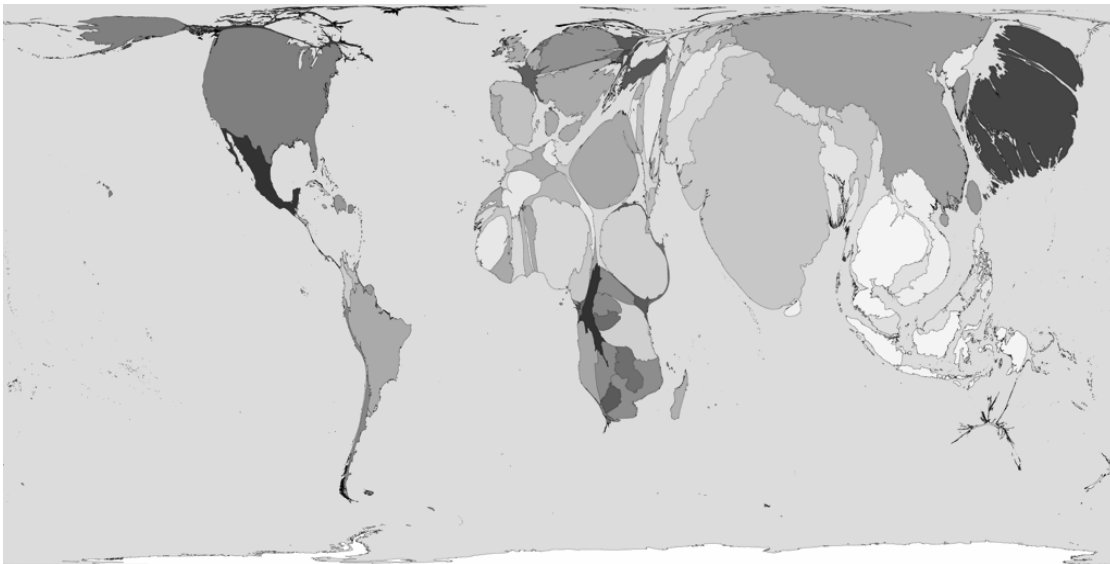


Figure 7.6: HCV (ICD-10 codes: B17.1, B18.2, not HCC) [http://www.worldmapper.org/display\\_extra.php?selected=388#](http://www.worldmapper.org/display_extra.php?selected=388#)

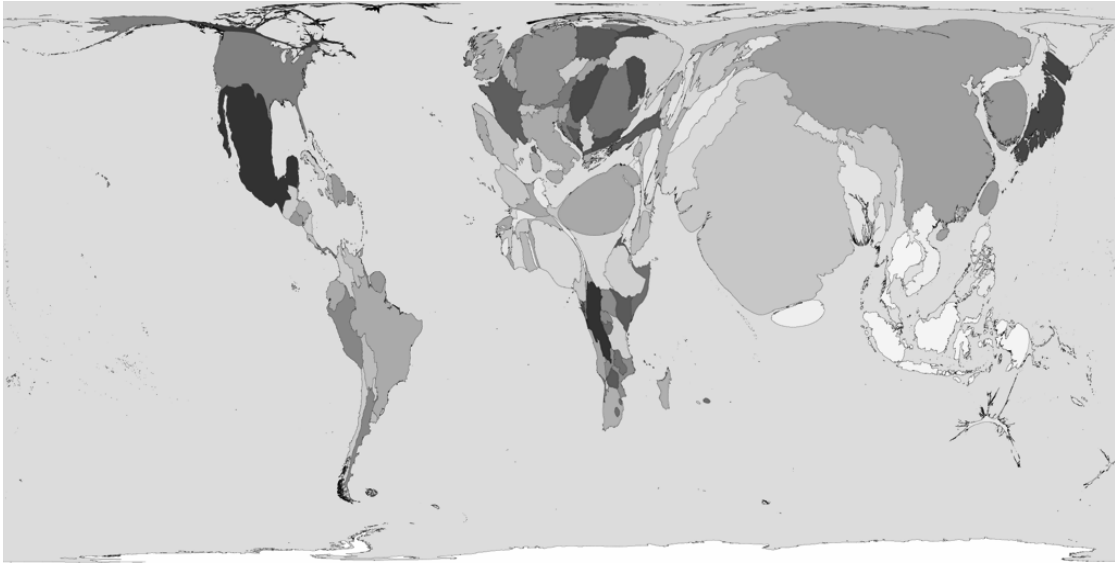


Figure 7.7: Cirrhosis (ICD-10 codes: K70-K74) [http://www.worldmapper.org/display\\_extra.php?selected=462](http://www.worldmapper.org/display_extra.php?selected=462)

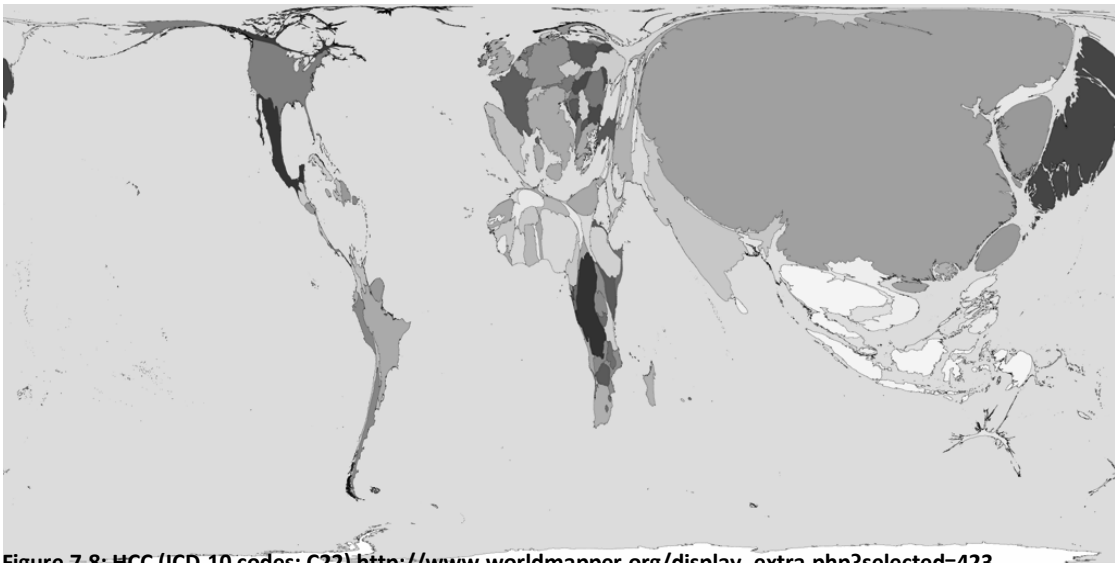


Figure 7.8: HCC (ICD-10 codes: C22) [http://www.worldmapper.org/display\\_extra.php?selected=423](http://www.worldmapper.org/display_extra.php?selected=423)

## 2.5 Modes of transmission

This broad variation between regions can be partially explained by the frequency and extent to which different risk factors have contributed to the transmission of HCV (Alter 2006; Wasley and Alter 2000). The initial spread of HCV is said to have started in the early 20th century through the use of unsterile injections, invasive surgical procedures and the transfusion of blood products (Esteban, Sauleda, and Quer 2008). In 1966, Dr J Garrott Allen of Stanford University Medical School published findings (Allen 1966) of a community-based survey on residents of the very deprived area of Los Angeles commonly known as “Skid Row.” It was reported that the residents use of alcohol, drugs and unsterilized needles meant that they were highly likely to be infected with Hepatitis B, which was discovered earlier in 1967 (Starr and Rosen 1998). In the midst of headlines claiming a “transfusion roulette” and that “Prison Drug and Plasma Projects Leave Fatal Trail” (Rugaber 1969), Allen sent some of his findings to Professor Richard Titmuss, a prominent social researcher based at the London School of Economics. In 1970, Titmuss published his classic work, “The Gift Relationship,” which was widely read in the USA and the UK.

Expanding on the growing anxiety around blood products and Allen’s findings, Titmuss discussed the values of private vs public healthcare. It was argued that blood donation in exchange for financial compensation would inevitably attract populations in most need of money. As was then as is now, it is those populations in more disadvantaged



circumstances that are likely to suffer disproportionately the burden of poor health, and in countries where private healthcare predominates (as in the USA), the poor are also less likely to have received treatment for infection. Moreover, the exchange of blood for money meant that those in most need of money had financial incentive to hide any disqualifying medical condition, or to provide misleading information when questioned (Titmuss 1970).

By the mid-1970s, it was becoming more apparent that some patients were being infected with hepatitis that was not caused by the A or B variant, but by what was to be discovered nearly a decade later as HCV. The UK was a major importer of US-based commercially-manufactured blood products and it was thought amongst medical circles that the imported blood supply was major factor, with a report to the UK government in 1979 suggesting:

*“[blood] products derived from paid donor plasma are known to carry a ten-fold increase in the risk of transmitting hepatitis over the risk from products derived from voluntary donations.”*

(Archer 2009)

However, the Government continued to purchase the commercial blood products, with disastrous consequences. It has since been estimated that by the late 1980s, between 2 and 10% of blood transfusions in developed countries were infected with HCV (Alter,

Purcell, Holland, Alling, and Koziol 1981; Colombo, Oldani, Donato, Borzio, Santese, Roffi, Vigano, and Cargnel 1987; Esteban, Gonzalez, Hernandez, Viladomiu, Sanchez, Lopez-Talavera, Lucea, Martin-Vega, Vidal, and Esteban 1990; Prati 2006). Most patients receiving clotting factor concentrates and blood transfusions (e.g. for haemophilia) were infected (Esteban, Esteban, Viladomiu, Lopez-Talavera, Gonzalez, Hernandez, Roget, Vargas, Genesca, and Buti 1989; Mannucci and Tuddenham 2001; Prati 2000; Prati 2002). In the UK, 4670 people treated with blood products in the 1970s and 1980s were infected with HCV, with 1243 also infected with HIV. Nearly 2000 people suffering haemophilia have died as a result. This was since been referred to by Robert Winston, a doctor and member of the House of Lords, as “the worst treatment disaster in the history of the NHS” (Dyer 2009).

Since the discovery of HCV, testing of blood donors (from 1992 onwards) has practically eradicated the spread of HCV through blood transfusions in many developed countries like the UK, with no further reported infections along this route since 1994 (Alter, Conry-Cantilena, Melpolder, Tan, Van Raden, Herion, Lau, and Hoofnagle 1997; Esteban, Saulea, and Quer 2008; Gonzalez, Esteban, Madoz, Viladomiu, Genesca, Muniz, Enriquez, Torras, Hernandez, and Quer 1995; Hutchinson et al. 2006; Prati 2006; Shepard, Finelli, and Alter 2005). In developing countries, however, the situation is the obverse. Harvey J. Alter has recently put forward that HCV is now an epidemic “of two worlds” (Alter 2005). This is because in poorer countries, at least in part because of financial constraints (Miller and Pisani 1999), contaminated blood transfusions and the

re-use of infected syringes are common, reported at 6.7 billion, or 39.3% of all injections, with an estimated 2.3 million new HCV infections per year, 200,000 HCV-related premature deaths, and 3.6 million years of life lost because of HCV-related liver complications (Hutin, Hauri, and Armstrong 2003).

Nowhere is this more evident than in Egypt (Figure 7.9), where infections targeting the liver have been likened to a curse (El-Zayadi 2004) and the prevalence of HCV has been estimated between 9% and over 20%, several times higher than any other country (Arafa, Hoseiny, Rekacewicz, Bakr, El-Kafrawy, Daly, Aoun, Marzouk, Mohamed, and Fontanet 2005; El-Raziky, El-Hawary, El-Koofy, Okasha, Kotb, Salama, Esmat, El-Raziky, Abouzied, and El-Karaksy 2004; Frank, Mohamed, Strickland, Lavanchy, Arthur, Magder, Khoby, Abdel-Wahab, Ohn, and Anwar 2000; Medhat, Shehata, Magder, Mikhail, Abdel-Baki, Nafeh, Abdel-Hamid, Strickland, and Fix 2002; Mohamed, Abdel-Hamid, Mikhail, Abdel-Aziz, Medhat, Magder, Fix, and Strickland 2005; Pybus, Drummond, Nakano, Robertson, and Rambaut 2003).

In rural areas and especially around the Nile delta, there have been staggering reports of HCV prevalence as high as 40-50% in the older adult population (Abdel-Aziz, Habib, Mohamed, Abdel-Hamid, Gamil, Madkour, Mikhail, Thomas, Fix, and Strickland 2000; Frank et al. 2000; Strickland 2006; Strickland, El-Kamary, Klenerman, and Nicosia 2008; Waked, Saleh, Moustafa, Raouf, Thomas, and Strickland 1995). Such is the extremity of the situation, Perz and Alter report:

“Although the incidence of new infections in Egypt appears to have decreased in recent years, HCV has continued to be transmitted via iatrogenic exposures, blood transfusion, and other means ... Thus, an enormous swath of the population has been left with chronic HCV infection and the impact of the HCV epidemic in Egypt, which is already substantial, will manifest itself for decades to come”

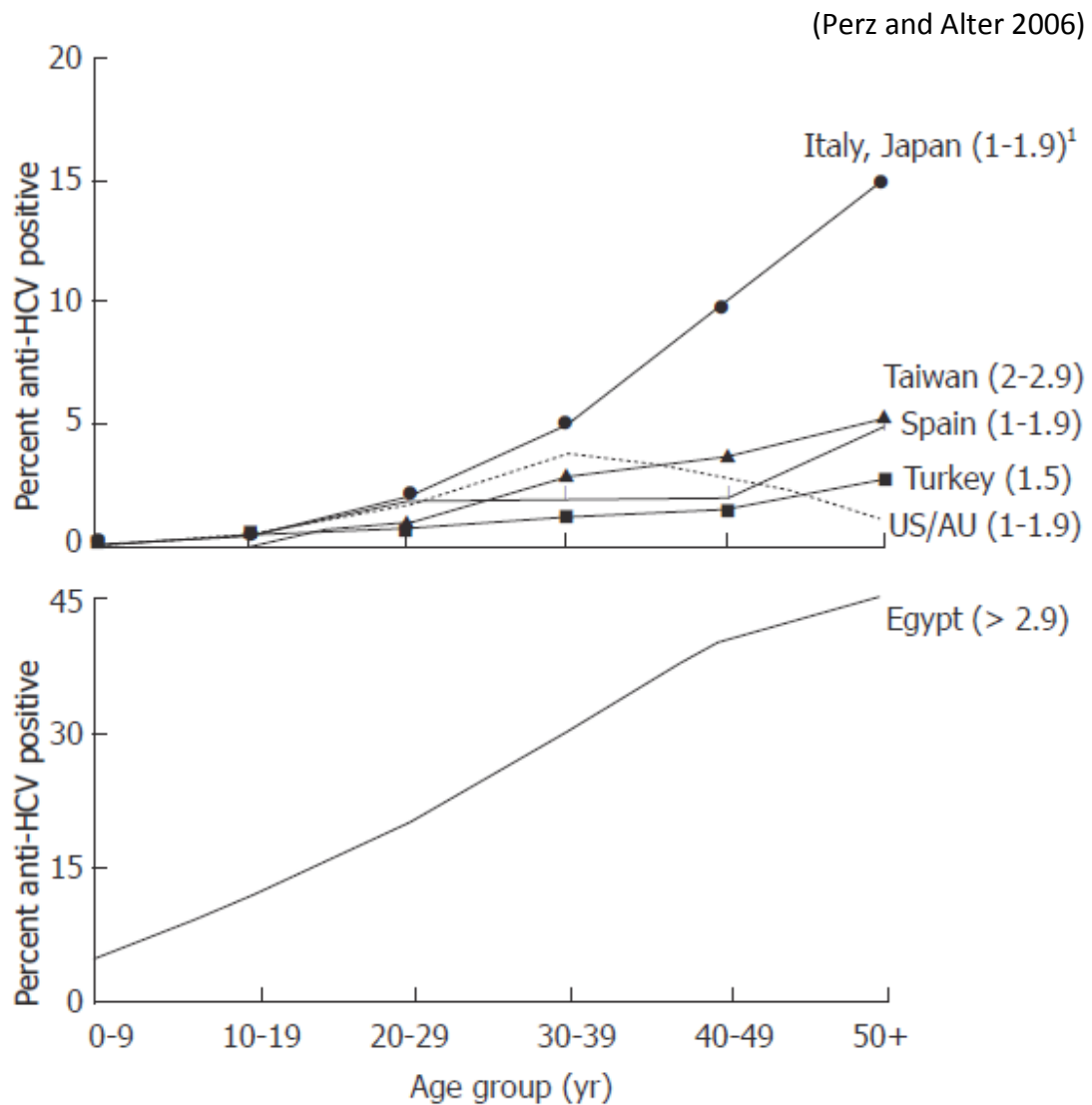


Figure 7.9: Estimated HCV prevalence by region: (Source: (Alter 2007))

Meanwhile, in the USA, Australia, the UK and other northern European countries, intravenous drug use (IDU) has become the dominant mode of HCV transmission for between 60 to 90% of infections during the last 35 years (Alter 2006; Alter 2007; Amon, Garfein, Ahdieh-Grant, Armstrong, Ouellet, Latka, Vlahov, Strathdee, Hudson, Kerndt, Des Jarlais, and Williams 2008; Crofts, Jolley, Kaldor, van Beek, and Wodak 1997; Dore, Law, MacDonald, and Kaldor 2003; Esteban, Sauleda, and Quer 2008; Hutchinson, Bird, and Goldberg 2005; Hutchinson et al. 2006; Pybus, Cochrane, Holmes, and Simmonds 2005; Wong 2000). The risk of infection through IDU is especially high during the first year (Sutton, Gay, Edmunds, Hope, Gill, and Hickman 2006), possibly when individuals might be trying IDU for the first time and most unaware of the dangers of sharing syringes. After 5 years of injecting, it is estimated that between 50% and 90% of individuals will have been exposed to HCV infection (Villano, Vlahov, Nelson, Lyles, Cohn, and Thomas 1997).

Other modes of transmission, although more unusual and less frequently cited within the literature include: vertical (mother-to-child); haemodialysis (kidney dialysis); sexual intercourse (especially if blood is present, for example during menstruation or anal sex); cocaine snorting; and unapparent percutaneous exposure. It is suggested that the UK has a similar rate of vertically transmitted infections to Western Europe at 3-7% (Gerner et al. 2006; Gibb, Goodall, Dunn, Healy, Neave, Cafferkey, and Butler 2000a; Hadzic 2001; Kowala-Piaskowska et al. 2004). HCV infection via sexual transmission, at approximately 5% (Leao, Teo, and Porter 2006), is considered to occur with much less efficiency

compared with transmission through repeated percutaneous exposures. Similar comparisons are drawn with HCV infection via perinatal and occupational exposures, (Goldberg, Cameron, Sharp, Burns, Scott, Molyneaux, Scoular, Downie, and Taylor 2001b; Rischitelli, Harris, McCauley, Gershon, and Guidotti 2001; Roy, Kennedy, Bagg, Cameron, Hunter, and Taylor 2003b; Shepard, Finelli, and Alter 2005; Thorburn, Dundas, McCrudden, Cameron, Goldberg, Symington, Kirk, and Mills 2001). (Bellentani et al. 2000) importantly note that there are lots of other risk factors which occur less frequently, however, and that many patients will have multiple risk factors for exposure that may interact to alter the course of the disease. (Alter 1997; Bellentani et al. 2000; Bronowicki, Venard, Botte, Monhoven, Gastin, Chone, Hudziak, Rihn, Delanoe, LeFaou, Bigard, and Gaucher 1997; Diseases 1998; Dore, Law, MacDonald, and Kaldor 2003; Gibb et al. 2000a; Gibb, Neave, Tookey, Ramsay, Harris, Balogun, Goldberg, Mieli-Vergani, and Kelly 2000b; Hadzic 2001; Haushofer et al. 2001; Hutchinson, Bird, and Goldberg 2005; Jenny-Avital 1998; Kowala-Piaskowska et al. 2004; Roy et al. 2003b; Ryder and Beckingham 2001b; Shepard, Finelli, and Alter 2005; Taylor, Goldberg, Hutchinson, Cameron, Gore, McMennamin, Green, Pithie, and Fox 2000; Thorburn et al. 2001; van Beek, Dwyer, Dore, Luo, and Kaldor 1998).

## 2.6 HCV prevalence within Europe

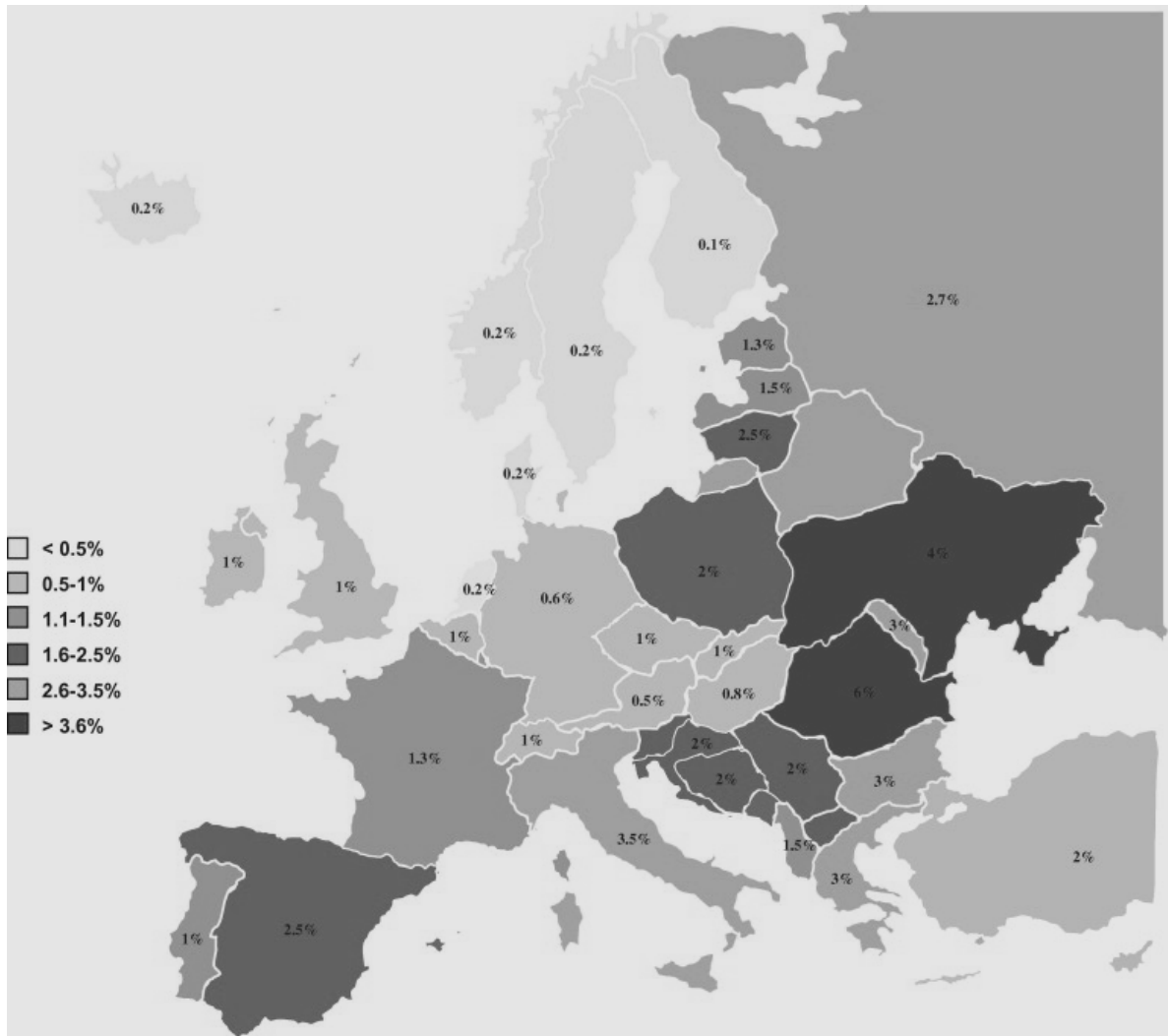


Figure 7.10: The north-south HCV prevalence gradient for selected European countries (Source: (Esteban, Saulea, and Quer 2008))

As has been briefly noted, there is further variation of HCV prevalence within Europe. Figure 7.10 illustrates that the Nordic countries, the UK and the Republic of Ireland, Portugal, the Netherlands, Germany and other countries of central-Europe tend to have relatively low prevalence ( $\leq 1\%$ ) when compared with Spain, Italy and many countries

to the east. This variation reflects contrasting patterns of HCV transmission in Europe (Morse 1995).

In the north, where the majority of individuals infected are between 30-50 years old, IDU has been the primary mode of transmission, surpassing blood transfusions and other routes (Deuffic, Buffat, Poynard, and Valleron 1999; Drucker, Alcabes, and Marx 2001; Giangrande 2000; Mizokami, Tanaka, and Miyakawa 2006; Morse 1995; Nakano, Lu, He, Fu, Robertson, and Pybus 2006; Nakano, Lu, Liu, and Pybus 2004; Pybus et al. 2003; Tanaka, Hanada, Orito, Akahane, Chayama, Yoshizawa, Sata, Ohta, Miyakawa, and Gojobori 2005; Tanaka, Kurbanov, Mano, Orito, Vargas, Esteban, Yuen, Lai, Kramvis, and Kew 2006).

Further south, in countries with prevalence above 1% such as Spain, Italy and Greece, blood transfusions are thought to be responsible for the HCV epidemic that started over 50 years ago and has led to a high prevalence in older people (20-30%). Long-term morbidity of this initial wave of infection is being realised with increasing rates of cirrhosis and HCC (Bourliere, Barberin, Rotily, Guagliardo, Portal, Lecomte, Benali, Boustiere, Perrier, and Jullien 2002; Martinot-Peignoux, Roudot-Thoraval, Mendel, Coste, Izopet, Duverlie, Payan, Pawlotsky, Defer, and Bogard 1999; Payan, Roudot-Thoraval, Marcellin, Bled, Duverlie, Fouchard-Hubert, Trimoulet, Couzigou, Cointe, and Chaput 2005; Roffi, Ricci, Ogliari, Scalori, Minola, Colloredo, Donada, Ceriani, Rinaldi, and Paris 1998; Roudot-Thoraval, Deforges, Girollet, Maria, Milliez, Pathier, Duval, and



Dhumeaux 1992; Savvas, Koskinas, Sinani, Hadziyannis, Spanou, and Hadziyannis 2005; Serra, Rodriguez, Del Olmo, Escudero, and Rodrigo 2003). This initial epidemic has been reinforced by an increase in IDU amongst younger people (Alter et al. 1981; Bellentani et al. 2005; Bellentani et al. 2000; Colombo et al. 1987; Drucker, Alcabes, and Marx 2001; Esteban et al. 1989; Frank et al. 2000; Mannucci and Tuddenham 2001; Nakano, Lu, Liu, and Pybus 2004; Prati 2000; Prati 2002; Shepard, Finelli, and Alter 2005).

Less seems to be known about the high prevalence reported in countries in the east of Europe and Russia, but appears mainly attributable to IDU (Kalinina, Norder, Vetrov, Zhdanov, Barzunova, Plotnikova, Mukomolov, and Magnius 2001; Ostrovski 2000; Rhodes, Singer, Bourgois, Friedman, and Strathdee 2005; Tallo, Norder, Tefanova, Krispin, Schmidt, Ilmoja, Orgulas, Pruunsild, Priimagi, and Magnius 2007).

## 2.7 HCV prevalence in the UK

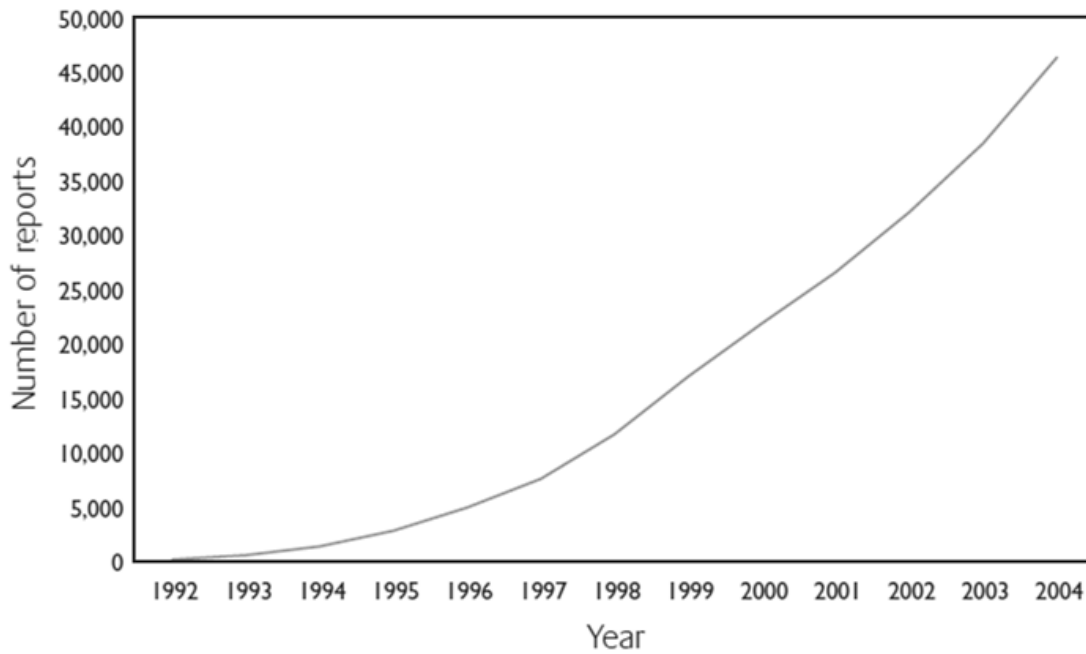


Figure 7.11: ‘Cumulative laboratory reports of hepatitis C infection from England: 1992 to 2004’ (Source: (Health Protection Agency 2005))

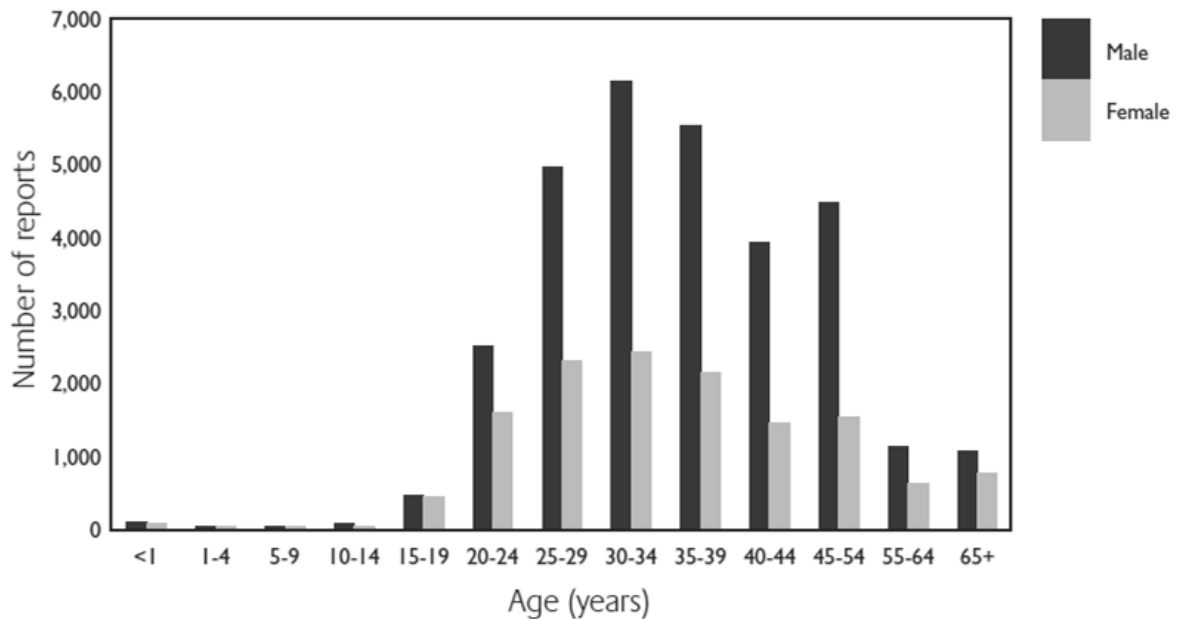


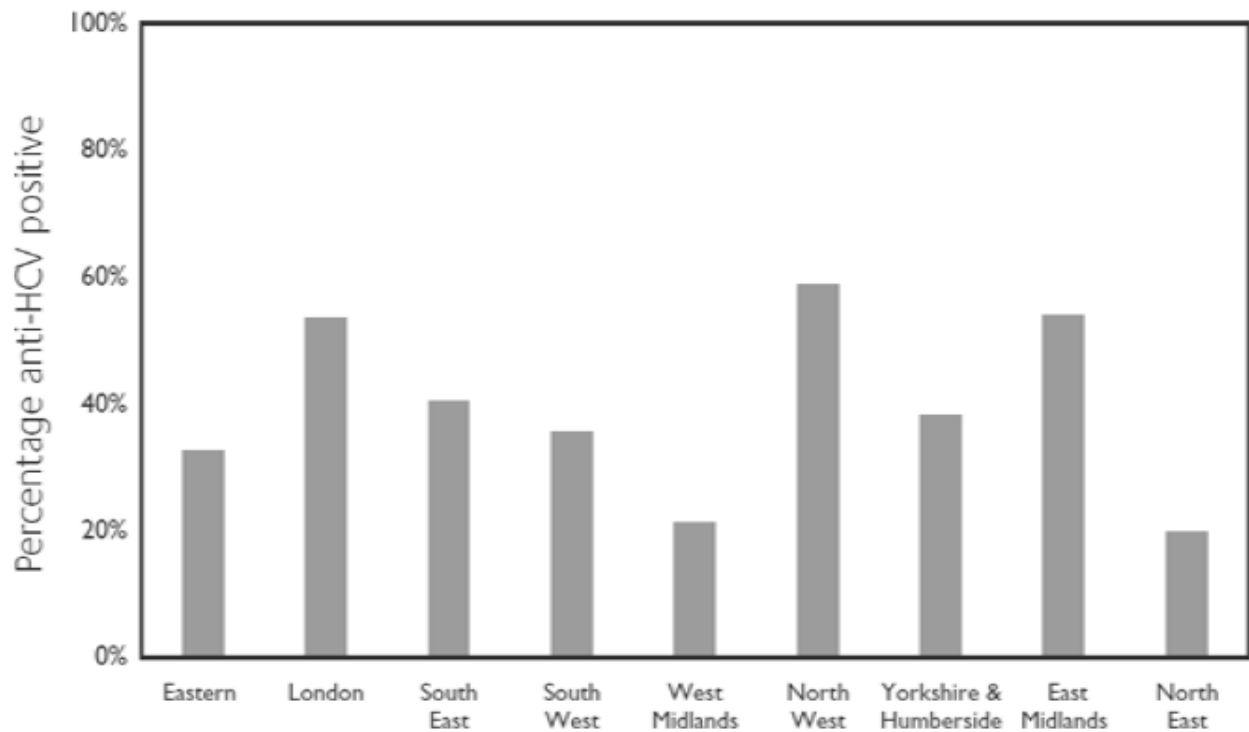
Figure 7.12: ‘Age and sex distribution of laboratory reports of hepatitis C infection from England: 1992 to 2004’ (Source: (Health Protection Agency 2005))

It is estimated that between 450,000 to 500,000 persons in the UK are infected with HCV (The Hepatitis C Trust and The University of Southampton 2005). It is estimated that 50,000 of these individuals live in Scotland alone, with between 1000 to 2000 new HCV infections every year acquired through IDU (Hutchinson et al. 2006; Scottish Government 2005). HCV laboratory reports in England have also been rising steeply over the last decade with no signs of decline (Figure 7.11).

Prevalence varies within the population, with men and persons aged between 25 to 40 years old more likely to be infected (Figure 7.12). As previously noted, the predominant mode of transmission has been IDU since the introduction of routine blood donor screening in the early 1990s (Christie 2000; Donahue, Munoz, Ness, Brown, Yawn, McAllister, Reitz, and Nelson 1992; Gerner et al. 2006; Hutchinson, Goldberg, King, Cameron, Shaw, Brown, MacKenzie, Wilson, and MacDonald 2004; Shepard, Finelli, and Alter 2005). Although no longer at risk from blood transfusions, there are a significant number of individuals that were infected during treatment for haemophilia in the 1970s and 1980s (Dyer 2009).

HCV prevalence has been estimated to vary considerably intra-nationally, albeit on rather large geographical scales. Much of this work has been focused on the IDU population, reflected in Figures 7.13 and 7.14. In England, the lowest reported prevalence amongst the intravenous drug using population was in the north, east and

West Midlands, whereas the London, the North West (e.g. Manchester and Liverpool) and the East Midlands (e.g. Birmingham) had high prevalence.



**Figure 7.13: ‘Geographic variations in the prevalence of HCV among current & former injecting drug users by English Region’ (Source: (Health Protection Agency 2005))**

In Scotland, the geographical variation of HCV prevalence appears more striking (Figure 7.14), though still at a very coarse spatial scale. Prevalence is estimated to be highest in the Greater Glasgow area, which is dominated by the city of Glasgow (the largest in Scotland with a population of over 600,000). The city of Glasgow has been the setting for many prevalence-related studies (Hutchinson, Bird, and Goldberg 2005; Hutchinson et al. 2004; Judd, Hutchinson, Wadd, Hickman, Taylor, Jones, Parry, Cameron, Rhodes, Ahmed, Bird, Fox, Renton, Stimson, and Goldberg 2005b; Sharp, Hutchinson, Goldberg,

Taylor, and Carr 2007; Taylor et al. 2000; Taylor, Hutchinson, Gilchrist, Cameron, Carr, and Goldberg 2008), though prevalence is also high in the area of Tayside in which the city of Dundee is also known to have high levels of IDU (Haw and Higgins 1998; Hay and McKegane 1996; McCarthy and Alan Pollock 1997) and is also the setting for some HCV-related research (McLernon, Donnan, Ryder, Roderick, Sullivan, Rosenberg, and Dillon 2009; Steinke, Weston, Morris, MacDonald, and Dillon 2002a; Steinke, Weston, Morris, MacDonald, and Dillon 2002b).

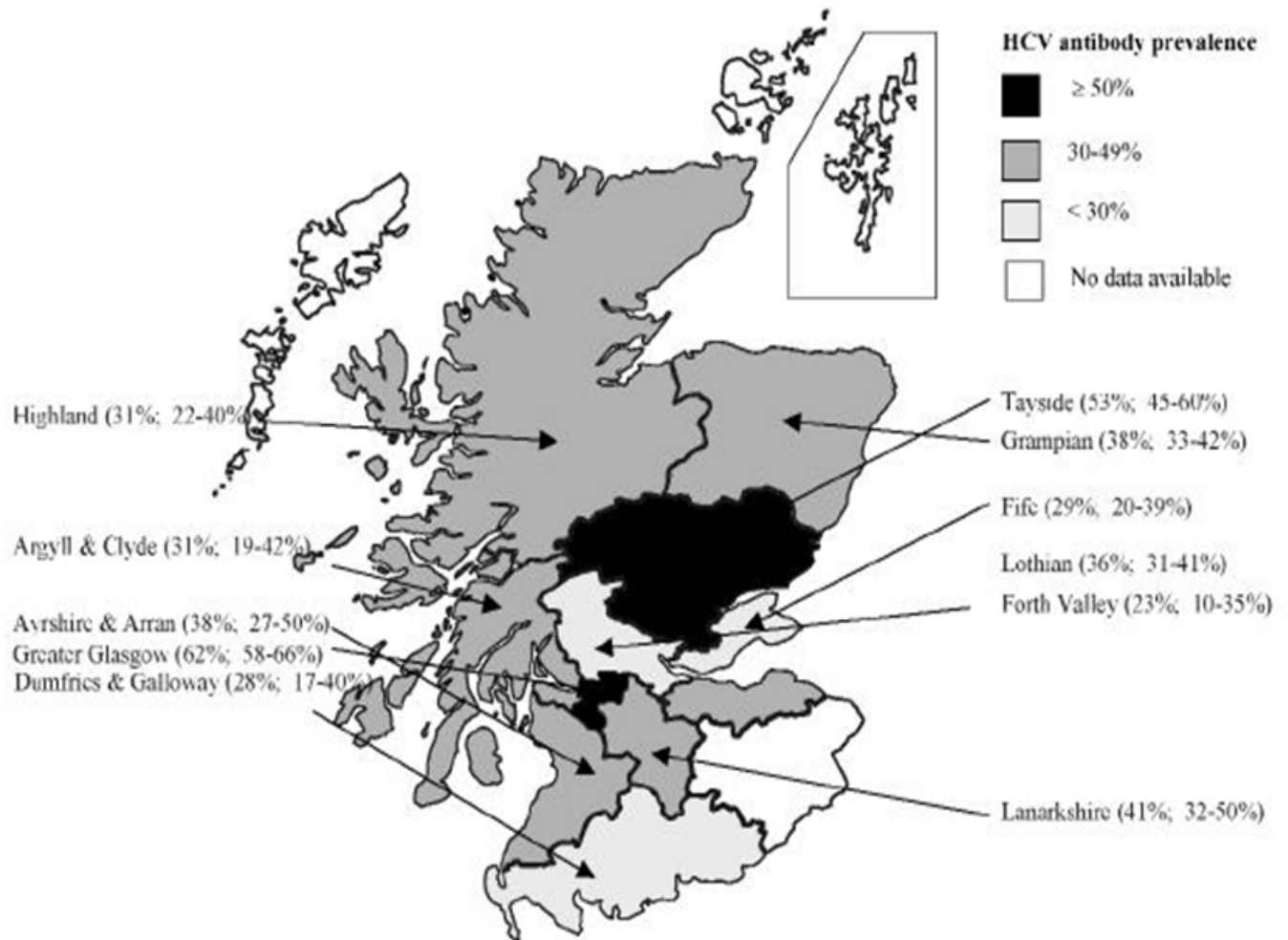


Figure 7.14: ‘HCV antibody prevalence (%; 95% CI) among 2141 IDUs in Scotland by health board area, 1999-2000’ (Source: (Hutchinson et al. 2006))

No small-scale research on HCV prevalence has yet been conducted within the UK, though these reports and other information would suggest variation. Of the current findings, the Health Protection Agency (HPA) (2005: 15) considers:

*“the reasons for this geographic variation are not known, but they may reflect current and historical variation in risk behaviours, in levels of injecting or in treatment provision between regions”*

The risk behaviour to which the report refers is IDU and there have been several aspatial studies attempting to determine the risk of HCV in particular population groups, including: young age; duration and frequency of IDU behaviour; sharing equipment; polydrug use; HCV prevalence among experienced IDUs; being a female IDU with an injecting partner; homelessness; having served a prison sentence; a recent uptake of injecting; and health intervention factors such as being in methadone treatment (Craine, Walker, Carnwath, and Klee 2004; Garfein, Doherty, Monterroso, Thomas, Nelson, and Vlahov 1998; Hagan, Thiede, Weiss, Hopkins, Duchin, and Alexander 2001; Hickman, Hope, Brady, Madden, Jones, Honor, Holloway, Ncube, and Parry 2007; Judd et al. 2005b; Mathei, Shkedy, Denis, Kabali, Aerts, Molenberghs, Van Damme, and Buntinx 2006; Villano et al. 1997).

Studies have also argued that IDU behaviour tends to be geographically concentrated into areas characterised by high rates of socioeconomic deprivation (Alter et al. 1999; Armstrong et al. 2006; Craine, Walker, Carnwath, and Klee 2004; Department of Health

2004a; Edeh and Spalding 2000; Hutchinson et al. 2004). This would suggest that HCV prevalence is also likely to be high amongst relatively poor populations in the UK, who tend to residentially concentrate within cheaper areas of inner cities (such as Glasgow and Dundee) characterised by high rates of deprivation and a multitude of other health problems (Boyle, Exeter, and Flowerdew 2004; Cox, Boyle, Davey, Feng, and Morris 2007; Cox, Boyle, Davey, and Morris 2007; Exeter, Boyle, Feng, and Boyle 2009; Exeter, Feng, Flowerdew, and Boyle 2005; Gray and Leyland 2009; Leyland 2005; Leyland, Dundas, McLoone, and Boddy 2007; Pearce and Boyle 2005; Stafford and Marmot 2003).

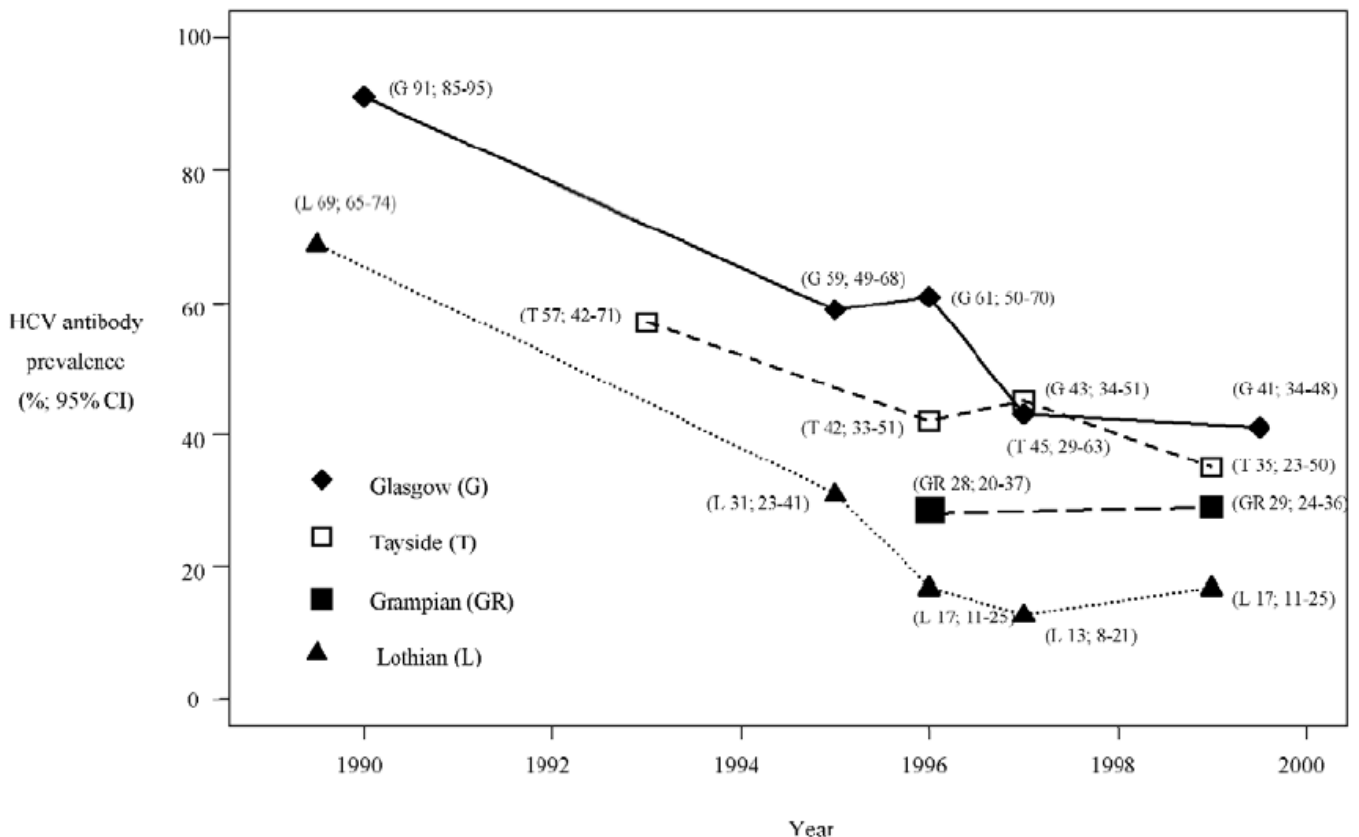


Figure 7.15: ‘HCV antibody prevalence (%; 95% CI) among young IDUs (aged under 25 years) in Scotland who had a named HIV test, 1989-2000’ (Source: (Hutchinson et al. 2006))

This is also reflected by the targeting of areas for harm reduction interventions, which promote syringe-exchange and opiate substitution therapy programmes. These have been suggested to have dampened the growing prevalence of HCV amongst persons involved with IDU during the mid 1990s (Figure 7.15). However, as previously noted, the incidence of new HCV infection amongst individuals partaking in IDU continues to increase in Scotland (Roy, Hutchinson, Wadd, Taylor, Cameron, Burns, Molyneaux, McIntyre, and Goldberg 2007) and other countries in Europe (Goldberg, Burns, Taylor, Cameron, Hargreaves, and Hutchinson 2001a; Hernandez-Aguado, Ramos-Rincon, Avino, Gonzalez-Aracil, Perez-Hoyos, De la Hera, and Ruiz-Perez 2001; Hickman et al. 2007; Jauffret-Roustide, Emmanuelli, Quaglia, Barin, Arduin, Laporte, and Desenclos 2006; Judd, Hickman, Jones, McDonald, Parry, Stimson, and Hall 2005a; Lucidarme, Bruandet, Illef, Harbonnier, Jacob, Decoster, Delamare, Cyran, Van Hoenacker, and Fremaux 2004; Miller, Mella, Moi, and Eskild 2003; Roy, Hay, Andragetti, Taylor, Goldberg, and Wiessing 2003a; Sutton, Edmunds, and Gill 2006).

Given therefore what is known about HCV infection in the UK: i) the predominant mode of transmission being IDU; and that ii) IDU behaviour is largely concentrated into socioeconomically deprived areas, it seems incomprehensible that there is not a single study exploring small-scale geographical variation of HCV prevalence. Only one study, which was not geographical, has come close and this utilised a measure of socioeconomic deprivation to show higher rates of detection (Hutchinson et al. 2004).



Perhaps also reflecting of the dearth of small-scale geographical studies, Hutchinson and colleagues suggest (2004; p.593):

*“in an era when resource rich countries are acutely aware of the association between poverty and disease, and actively promote policies to reduce inequity, few studies have examined the possible links between deprivation and HCV infection.”*

The true extent to which this gap in the literature is significant remains unknown. However, there is a considerable history of research linking deprivation and health in many other contexts, from which it is not difficult to speculate that any successful policy for tackling the burden of the HCV epidemic will probably have to understand association with relative poverty. For instance, in the 19<sup>th</sup> century William Farr showed that populations in Liverpool, Manchester and London experienced poorer health than those in the north east (Farr 1837, 1885). Later in the 19<sup>th</sup> century, Durkheim reported that persons with fewer social connections were more likely to commit suicide than those with a more abundant supply of friends and networks (Durkheim 1897). It has since been argued that persons lacking social connections are likely to occupy less favourable socioeconomic position (Ioannides and Loury 2004) and depend more on those who live near them (Forrest and Kearns 2001).

Suicide has since been shown to occur significantly more often in areas of high socioeconomic deprivation in Scotland, particularly Glasgow (Boyle, Exeter, Feng, and Flowerdew 2005; Exeter, Boyle, Feng, and Boyle 2009; Exeter, Feng, Flowerdew, and

Boyle 2005). Dorling and colleagues have demonstrated that levels of poverty in London reported by Charles Booth in 1896 strongly predict mortality in the same areas in 1991 (Dorling, Mitchell, Shaw, Orford, and Davey Smith 2000). The higher levels of smoking in Greater Glasgow relative to the rest of Scotland have been attributed to high levels of socioeconomic deprivation (Gray and Leyland 2009).

Wilkinson famously shows an association between the level of income inequality, or relative deprivation inequality within countries and mortality and Boyle and colleagues demonstrate comparable findings at a local level (Boyle, Norman, and Rees 2004; Marmot and Wilkinson 2001; Wilkinson 1997; Wilkinson and Pickett 2006), though others still favour outright more materialistic explanations (Lynch and Smith 2002; Lynch and Kaplan 1997; Lynch, Smith, Kaplan, and House 2000). In a very high profile report, Diez Roux and colleagues demonstrated that the higher the socioeconomic deprivation experienced locally, the greater the risk of developing coronary heart disease (Diez Roux, Merkin, Arnett, Chambless, Massing, Nieto, Sorlie, Szklo, Tyroler, and Watson 2001). Coleman and colleagues have shown repeatedly that less favourable socioeconomic position is related to cancer survival (Coleman, Babb, Sloggett, Quinn, and De Stavola 2001; Coleman, Rachet, Woods, Mitry, Riga, Cooper, Quinn, Brenner, and Estève 2004; Jeffreys, Rachet, McDowell, Habib, Lepage, and Coleman 2006; Rachet, Woods, Mitry, Riga, Cooper, Quinn, Steward, Brenner, Estève, and Sullivan 2008; Woods, Rachet, and Coleman 2005; Woods, Rachet, and Coleman 2006).

The 'Black Report' of 1980, authored by Sir Douglas Black, is perhaps the most important source of evidence and a catalyst for many researchers interested in medical/health geography. It displayed evidence for what many already suspected, and discussed at length hypotheses of how those poorer individuals in society end up suffering the greatest burden of ill health and worst chances of survival (Black, Morris, Smith, and Townsend 1988; Macintyre 1997). The 'socioeconomic gradient' has since passed into terminology as fact (Wilkinson and Marmot 2003). But the findings were 'unpalatable' and ignored by the UK government of the era, which resulted it being published on a Bank Holiday weekend, with only 260 copies made available on the day for the media (Bartley, Blane, and Davey Smith 1998; Davey Smith, Bartley, and Blane 1990; Sim and Mackie 2006).

Regrettably, governments have been repeatedly slow to act. An independent enquiry has condemned the same government that attempted to suppress the Black Report, for procrastination after being informed of the contaminated blood products commercially manufactured in the US from risky donors. Kenneth Clarke, the Secretary of State for Health at the time, claimed in Parliament that:

*"there is no evidence that AIDS is transmitted by blood products"*

(Archer 2009)

Of course, the cause of AIDS was identified in 1984 as the virus now widely known as 'Human Immune-Deficiency Virus', or HIV (Potter, Binns, and Elliott 2004). Thousands of people in the UK with haemophilia and others having blood transfusions were infected not only with HIV, but also with HCV (e.g. Dame Anita Roddick, founder of Body Shop was infected with HCV through a blood transfusion given in 1971 whilst giving birth (Roddick 2007)). On this 'horrific tragedy' (Dyer 2009), Archer and the panel of the independent inquiry write:

*"Campaigners have been working for years to raise awareness of the plight of [haemophilia] patients in order to present the case for an adequate and reasonable response to their suffering and that of their families. This suffering has never been sufficiently acknowledged, nor the consequences of it addressed. It affected, and continues to affect, all aspects of the victims' lives – physical, emotional, social and, of course, financial... Long after alarms had been sounded about the risks of obtaining paid-for blood donations from communities with an increased incidence of relevant infections, such as prison inmates, this practice continued. It is difficult to avoid the conclusion that commercial interests took precedence over public health concerns... We are dismayed at the time taken by Governmental and scientific agencies to become fully alive to the dangers of Hepatitis C and HIV, and also by the lethargic process towards self-sufficiency in blood products."*

(Archer 2009)

Such lethargy seems to have continued with regards to tackling the HCV epidemic, not only on the part of the UK government but also those in other countries. An argument has been positioned by various authors as to why governments have been slow to react (Edlin 2004; Hopwood and Treloar 2003) along the lines that whilst the HIV/AIDS epidemic has been highly visible in the 'Western' world, mobilising activists, the media, and people affected by the virus, HCV has remained largely the concern of public health officials and of a relatively small number of people living with symptomatic HCV. This is put down to the asymptomatic nature of HCV and its concentration amongst people with a history of IDU (who are often marginalised and criminalised).

Whereas the fight against HIV/AIDS is visible amongst affluent societies, due in no small way to the action by gay activists, liberal politicians, concerned health professionals, the media, and so-called awareness campaigns (popular music concerts sensu Live Aid), the fight against HCV seems to lack such initiatives. Indeed, until as recently as 2002, policy produced by the US National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) virtually ignored the need for prevention and treatment strategies, expansion of substance abuse prevention or treatment, the implementation of syringe exchange programmes, removal of legal barriers to syringe access, community-based outreach, or HCV counselling, testing and treatment programmes for IDUs or incarcerated persons (Edlin 2004). Bastos (2006: 1) puts this down to:

*“a mixture of denial, prejudice, lack of a democratic media, of political will, of funds and of qualified personnel.”*

Hopwood & Treloar (2003: 16) argue a similar case:

*“The illegal status of injecting drug use throughout Australia, and inadequate concern regarding the likelihood that hepatitis C could cross-over into mainstream Australia are reasons given for why governments have been slow to respond to a mounting health crisis.”*

In the UK, recent government support has been viewed as insufficient according to William Rosenberg, Professor of Hepatology (UCL):

*“It took two years to get a campaign from the government which is funded to the tune of £2million over two years- compared to the £40million pledged every year for ten years, to persuade us to switch to digital TV.”*

(The British Society of Gastroenterology 2006)

The looming wave of liver-related morbidity and mortality and perceived lack of action among policymakers, not least in the lack of funding for awareness campaigns and dearth of research on the links between health-related outcomes of people with HCV, deprivation and other social risk factors, is made all the more clear in the next section.

## 2.8 Losing the fight against HCV?

Figure 7.1 (referred to at the beginning of the chapter) illustrates the situation with regards to tackling the HCV epidemic in the UK. The majority of persons infected remain undiagnosed. Less than half of those diagnosed are not referred to an HCV specialist centre. Of those that are referred, only a proportion has actually attended their specialist appointment, whilst some have been unable to adhere to follow-up appointments. Those that do attend, only a fraction are eligible for treatment and only some of those actually receive any (The Hepatitis C Trust and The University of Southampton 2005). As has already been emphasised, the biological, social and financial consequences of leaving HCV unchecked and untreated could be profound. Thus, it is imperative not only to prevent further infection, but to diagnose and treat those people that are currently infected before the development of liver-related complications.

HCV testing should be offered to all individuals at high risk of being infected, for example IDUs, people who received a blood transfusion or blood products prior to 1991, and HIV infected individuals (Alberti et al. 2005; Pembrey, Newell, and Tovo 2005; Pugatch, Anderson, O'Connell, Elson, and Stein 2006; Thimme, Spangenberg, and Blum 2005). Routine screening in the general population is not recommended (Pembrey,

Newell, and Tovo 2005), as it is supposed that this may consolidate and emphasise the already apparent stigma associated with an HCV diagnosis. This generally includes testing women in pregnancy, which is limited to areas of high HCV prevalence (Hadzic 2001). Another explanation for this is because there is no proven intervention for vertical/mother-to-child HCV transmission available (Dore, Law, MacDonald, and Kaldor 2003; Hadzic 2001). Nevertheless, it is important to identify HCV infected women to enable the best possible management of their infection and to prevent further transmission (Pembrey, Newell, and Tovo 2005).

Diagnosis of HCV is performed via screening tests using enzyme linked immunosorbent assays (ELISA) with recombinant viral antigens on patients' serum (Ryder and Beckingham 2001a). In acute hepatitis there is usually a period 5-6 weeks between onset of clinical illness and seroconversion for about 80% of patients (Committee on Infectious Diseases 1998), which means a person may test negative even though they do have HCV. Indeed, this marks another discrepancy within the literature as (Ryder and Beckingham 2001a) report the time period can be much longer at three months. Several other tests are required for diagnosis, involving a polymerase chain reaction (PCR) test to identify current circulating virus and more sophisticated PCRs to identify the viral load (amount) and the genotype of the virus (The Scottish Executive 2006). Early detection provides the opportunity to counsel the patients regarding disease progression and transmission (Pugatch et al. 2006) and early referral to treatment,



which strong evidence has shown to decrease the chances of progressing to HCV from 80% to 50% (Ryder and Beckingham 2001a).

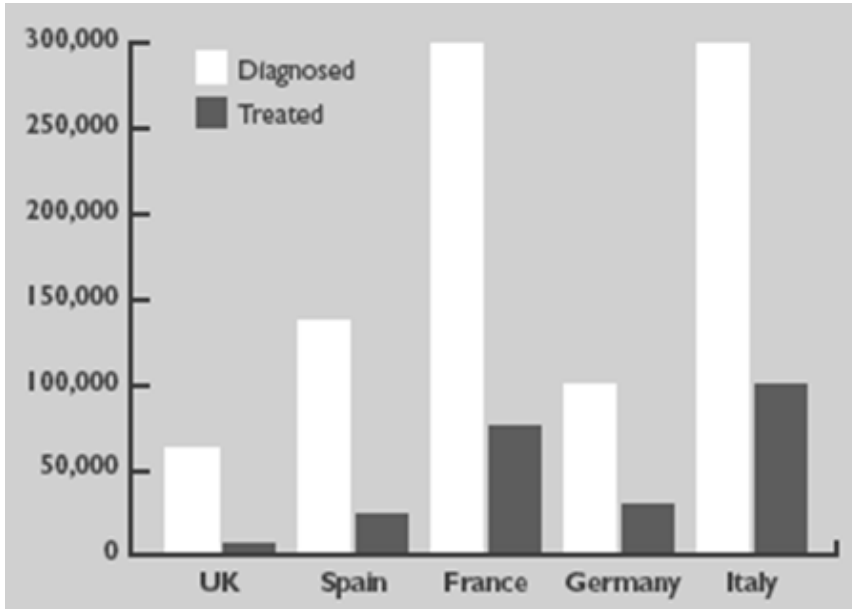


Figure 7.16: European figures for patients ever diagnosed and treated for HCV (Source: (The Hepatitis C Trust and The University of Southampton 2005) )

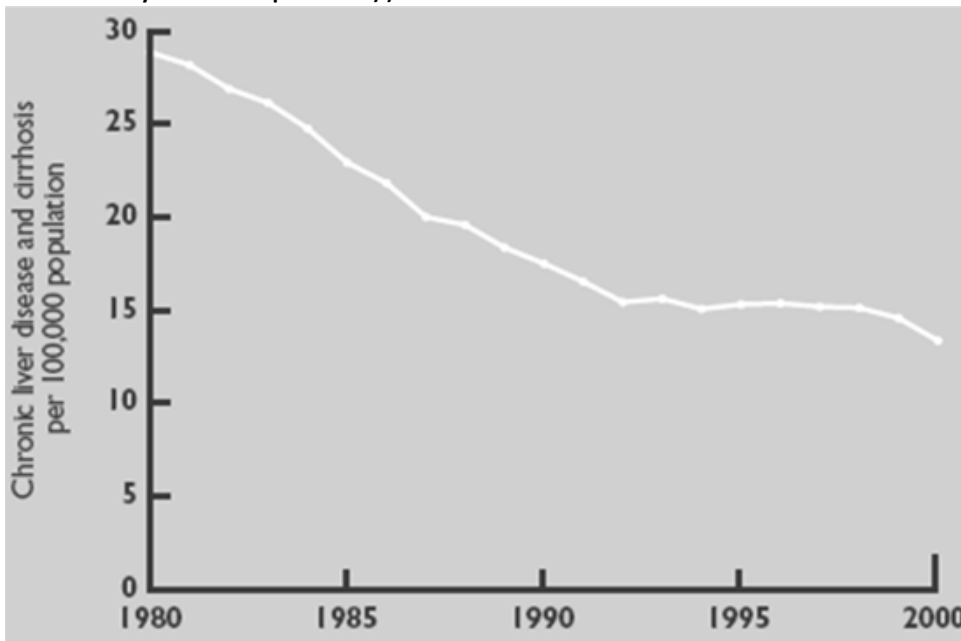


Figure 7.17: Prevalence of chronic liver disease and cirrhosis in France (Source: (The Hepatitis C Trust and The University of Southampton 2005) )

In contrast to the UK, many European nations such as France have managed to diagnose and treat a considerably greater proportion of infected individuals (Figure 7.16). Detection rates in France have more than doubled in the last ten years. Patient awareness is also now high – four times higher than in Britain, with 56% of people with HCV now aware that they have the disease as compared to 24% in 1994. The number of people suffering from chronic liver disease and cirrhosis has begun to fall again since the implementation of blood screening (Figure 7.17) (The Hepatitis C Trust and The University of Southampton 2005).

This success has been attributed to numerous factors including (not an extensive list): ‘free testing’ days; a strong political commitment with clearly planned and well-funded action plans; anonymous testing; multi-media campaigns (Figure 7.18); the creation of surveillance systems to determine the extent of the problem and measure the impact of interventions (The Hepatitis C Trust and The University of Southampton 2005). As a result, French services have treated 75,000 people over the last 15 years – nearly 12.5 times those in the UK. Similar action has been taken in Spain, Germany, and Italy, where in the 500 centres (approximately five times as many as the UK, despite a similar size of total population) in the latter country offer specialist care and have the authority to prescribe treatments. High levels of public awareness in Italy and Spain also mean that 60% and 80% respectively of patients are referred directly to specialists (The Hepatitis C Trust and The University of Southampton 2005).



Figure 7.18: HCV Awareness Poster in France (Source: (The Hepatitis C Trust and The University of Southampton 2005) )

Awareness of HCV in the UK is poor, not only amongst the public, but the medical profession (d'Souza, Glynn, Alstead, Osonayo, and Foster 2004). In 2002, The Department of Health called for an HCV awareness campaign to be urgently initiated. The 'Face It' awareness campaign that materialised been criticised for inappropriate timing and a lack of financial support, exemplified by the previous quotation by Rosenberg, and furthermore:

*“The current campaign is pejorative and basically says ‘face your guilty past’ when what we should be saying is it doesn't matter how you got infected, you need to get treated.”*

(Rosenberg 2006)

The ‘Face It’ campaign may not be delivering the right message. In the UK, the General Practitioner (GP) is the ‘gatekeeper to the NHS’ or the ‘first medical contact’ within the healthcare system for most individuals (Cox 2006). It is usually through a GP referral that patients are referred to specialist services, such as those associated with treating HCV infection. However, with Rosenberg’s interpretation of the ‘awareness’ campaign and the ongoing problem of IDU-related stigma associated with HCV, it is difficult to believe that this will have done much to reduce discriminative beliefs among GPs who have been reported to often assume patients to be drug users, who are then personally blamed for acquiring the disease, held liable for perpetuating the epidemic and perceived as irresponsible and unworthy of further treatment (Paterson, Backmund, Hirsch, and Yim 2007).

In Australia, where a considerable amount of research has been conducted, a lack of awareness in the medical profession has been shown to lead to insensitive delivery of diagnosis by doctors who assume the infection was the result of ‘deviant’ behaviour. The same attitude filters down to the healthcare workers, which results in a poor quality of treatment (Golden, O'Dwyer, and Conroy 2005; Hopwood and Treloar 2003). The All-

Party Parliamentary Hepatology Group audit of the HCV Action Plan in England states that HCV awareness remains low despite the efforts of the FaCe It campaign:

*“A positive diagnosis can have significant financial implications, for example in obtaining insurance or a mortgage. Many people, therefore, may be deterred from seeking a test, unless it can be done anonymously. Given the importance of increasing diagnosis and making testing as accessible as possible, we are both disturbed and surprised that not all PCTs know about anonymous testing facilities in their area. Some PCTs showed very little awareness of the issue by simply answering ‘GUM clinics’ [Genito-Urinary Medicine clinics, to the question – Does the PCT know where anonymous testing facilities for hepatitis C are available?], when in fact some GUM clinics will not test for hepatitis C on the grounds that it is not a sexually transmitted disease.”*

(The All-Party Parliamentary Hepatology Group 2006)

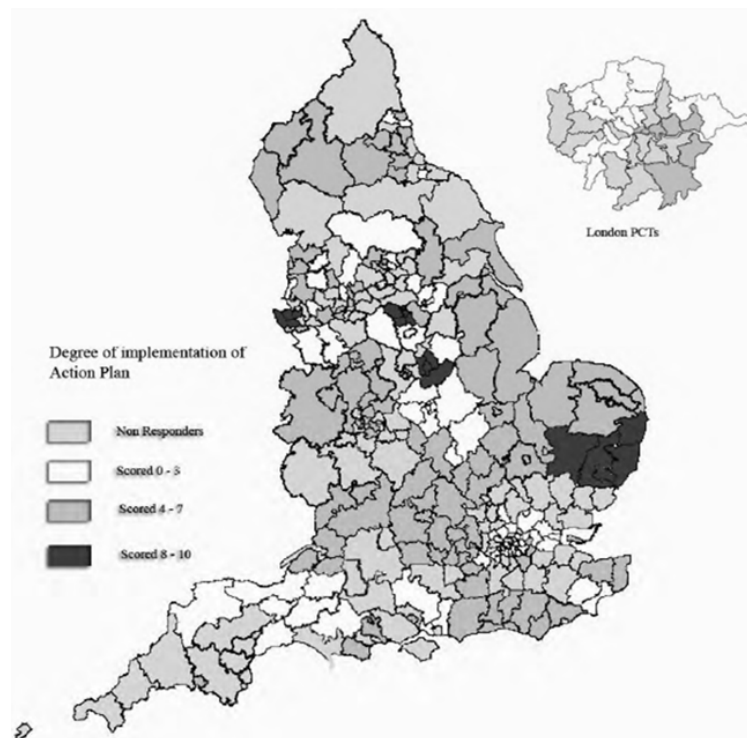
Both the HCV Action Plan for England (Department of Health 2004b) and that for Scotland (The Scottish Government 2005) report that although the UK has a relatively low prevalence in comparison to many other countries, it is certainly one of the worst in Europe when it comes to every aspect of dealing with HCV. The All-Party Parliamentary Hepatology Group concluded:

*“With just 8% of responding PCTs implementing the Action Plan [for England] in what we consider to be an effective manner and significant delays in almost half of responding NHS Hospital Trusts, we have to conclude that, more than 18 months since its publication, the Action Plan is failing to deliver the services that hepatitis C patients have a right to expect..... We have voiced our concern in the past that the Action Plan had no budget, no targets and no timetable and without them it would fail..... Unless vastly more vigorous efforts are made now at local level by PCTs, encouraged by targets and a timetable set out nationally by the Department of Health, we predict that hepatitis C will in the future become a crushing burden to our health service and that we will look back and know we could have prevented that happening.”*

(The All-Party Parliamentary Hepatology Group 2006)(pp.2, 3, 15)

It is also worrying that the two thirds of Primary Care Trusts (PCTs hereafter) have been reported as having made little effort to ascertain the number of people with HCV in their respective areas, the numbers diagnosed, the number likely to be diagnosed shortly and the number likely to remain undiagnosed in the absence of increased testing. Moreover, less than half of the PCTs had an estimate of numbers of patients requiring treatment. Therefore, how did the other half negotiate contracts with the hospitals to provide the treatment and how were the hospitals able to plan staffing in liver units (The All-Party Parliamentary Hepatology Group 2006)? Perhaps this simply is not possible with the limited resources available to PCTs who may be doing a very good job

in gross circumstances (See Figure 7.19 for degree of Action Plan implementation in England). However, HCV surveillance systems in other European countries have been demonstrated to aid planning of proper services and staff for testing, for hospital appointments and for treatment. At this present moment, the UK has no such surveillance system to compare, which may lead to a mixture of bottle-necks in some areas and overcapacity in others.



**Figure 7.19: The degree of implementation of the Hepatitis C Action Plan for England by PCT area (Source - The All-Party Parliamentary Hepatology Group, 2006)**

The 'patient journey' for a newly diagnosed HCV patient typically involves the following stages: a referral by a GP; a hospital appointment with a HCV specialist; a recommendation for treatment; and finally the start of treatment. Other investigations, such as further blood tests and ultrasound scans may also lengthen this process. However, the current average waiting time from GP referral to the start of treatment is 25 weeks, which at almost half a year is too long. It is more than possible that a patient could progress from vital-to-treat cirrhosis to too-late-to-treat decompensated liver disease or liver cancer during this period of time (The All-Party Parliamentary Hepatology Group 2006). Ideally, the earlier a person is screened using accurate serologic tests, the larger the window of opportunity to counsel the infected persons regarding the likely disease progression and transmission (Pugatch et al. 2006). Treatment of acute HCV may reduce the risk of chronicity and treatment of HCV early on would lessen the chances of fibrosis many years later, so early treatment is advised where possible (Alberti et al. 2005). However, (The Hepatitis C Trust and The University of Southampton 2005) report that less than half of all patients who are detected are even referred to a specialist centre.

The remainder are said to either never return to the GP to obtain blood test results or fall out of the system due to (again) a poor awareness of the long-term consequences of the virus. (Walley et al. 2005) showed that in a study of knowledge of and interest in HCV treatment at a methadone clinic in the USA, only 34% of those surveyed knew about treatment and 30% had already been evaluated for treatment. Moreover, men



were five times more likely to be aware of treatment possibilities than women, whilst Whites, were seven times and Latinos were about six times more likely than African-Americans to know about HCV treatment. (Davis, Rhodes, and Martin 2004; Davis and Rhodes 2004) report similar findings, emphasising HCV is poorly understood by most IDUs and that misunderstandings are regularly contextualised by wider uncertainty and indeterminacy concerning HCV knowledge and only made sense of in relation to HIV. No other study of this type in the UK has been found up to the time of writing.

According to John Dillon (2004), Consultant Hepatologist and Gastroenterologist at Ninewells Hospital and Medical School (Dundee), the best possible treatment for HCV infection is:

*“a skilled multidisciplinary team delivering combination PEG interferon and ribavirin therapy to well-informed, motivated patients who are supported throughout therapy”*

(Dillon 2004)

The duration of this treatment is based upon the diagnosis of a particular genotype. In general, treatment involves a self-subcutaneous injection of PEG-IFN once a week in combination with 1000mg of ribavirin (patients > 75kg 1200mg) orally per day. In the case of genotypes 2 and 3, 6-months therapy with PEG-IFN and 800mg ribavirin is sufficient (Bhopale and Nanda 2005). High sustained virological response (SVR) rates over 97% have been reported (Jaeckel, Cornberg, Wedemeyer, Santantonio, Mayer,

Zankel, Pastore, Dietrich, Trautwein, and Manns 2001; Kamal, Fouly, Kamel, Hockenjos, Al Tawil, Khalifa, He, Koziel, El Naggar, and Rasenack 2006a; Kamal, Moustafa, Chen, Fehr, Moneim, Khalifa, El Gohary, Ramy, Madwar, and Rasenack 2006b) for acute infection. SVR rates are lower if patients are detected later into the course of the infection (the chronic stage), ranging from 42-52% for those infected with genotype 1, to 76-82% for genotypes 2 and 3 (Fried, Shiffman, Reddy, Smith, Marinos, Goncalves, Haussinger, Diago, Carosi, and Dhumeaux 2002; Hadziyannis, Sette, Morgan, Balan, Diago, Marcellin, Ramadori, Bodenheimer, Bernstein, and Rizzetto 2004; Manns, McHutchison, Gordon, Rustgi, Shiffman, Reindollar, Goodman, Koury, Ling, and Albrecht 2001; Zeuzem, Hultcrantz, Bourliere, Goeser, Marcellin, Sanchez-Tapias, Sarrazin, Harvey, Brass, and Albrecht 2004). The cost of investigation and treatment with combination therapy, per patient, is estimated to cost in the region of £7,500 for 6 months treatment, or £14,000 for 12 months (Howie and Hutchinson 2004).

However, even if a person is successfully referred to a specialist, there are numerous reasons why they might be denied treatment. The Hepatitis C Trust website contains this message:

*“Taking interferon and ribavirin treatment requires a significant commitment of time and effort. It is not like popping a couple of aspirin to relieve a headache. It involves a lot of trips to hospital over many months, a lot of tests and you may or may not experience side effects.”*

There are numerous potentially serious adverse effects associated with HCV therapy that complicate the decision to treat patients. Interferon can cause (but not limited to) bone marrow suppression, flu- like symptoms, depression and other mood disorders, nausea, alopecia, anorexia, weight loss, and thyroid disorders (Lieb, Engelbrecht, Gut, Fiebich, Bauer, Janssen, and Schaefer 2006). (Fraenkel, McGraw, Wongcharatrawee, and Garcia-Tsao 2006) reports that these adverse effects may be severe and lead to discontinuation of therapy in 10-14% of the treated cases. It is advised that treatment should be deferred in patients with moderate to severe depression until the condition improves (Alberti et al. 2005). Ribavirin has a risk of causing haemolytic anaemia, which is can precipitate myocardial infarction in patients with coronary artery disease. Ribavirin is also a significant teratogen *“necessitating the use of contraception in patients with childbearing potential, further complicating the decision-making process in younger patients”* (Fraenkel, McGraw, Wongcharatrawee, and Garcia-Tsao 2006) (pp.2).

Psychiatric distress is reported as the main reason for delaying or discontinuing treatment, however, few studies have addressed the problem of anxiety disorders, which are also likely to play a crucial role in treatment adherence (Golden, O'Dwyer, and Conroy 2005). A psychiatric study found that patients with HCV develop cognitive impairment after just 3 months of low-dose treatment with IFN-Alpha and that the cognitive impairment was not correlated with symptoms of depression or anxiety. It is

advised close monitoring is required for HCV treatment (Lieb et al. 2006). It is unknown whether this standard of monitoring is consistent across all parts of the UK. It is normal that people with HCV often have reduced physical and social functioning, reduced mental and general health, and limitations in physical and emotional roles and reduced energy and increased fatigue (Hopwood and Treloar 2003).

As the majority of new and existing individuals infected with HCV are related to IDU, a population where the prevalence of psychiatric comorbidity is already high pre-HCV treatment (current and former IDUs on methadone maintenance therapy are ten times more likely to have a psychiatric disorder than the rest of the population - (Loftis, Matthews, and Hauser 2006)), it is not uncommon for IDUs to be considered poor candidates for therapy and denied treatment because of concerns regarding increased psychiatric disease, adherence, and reinfection (Broers et al. 2005; Edlin 2002; Edlin, Kresina, Raymond, Carden, Gourevitch, Rich, Cheever, and Cargill 2005; Sylvestre, Litwin, Clements, and Gourevitch 2005).

Furthermore, there are further barriers to accessing treatment for HCV-HIV coinfecting patients and also those with a history of IDU, including: being female, young age, and a lack of methadone substitution therapy. (Sylvestre, Litwin, Clements, and Gourevitch 2005) reason that it may “because HCV is generally not an emergency to treat, stabilizing substance use behaviours before initiating HCV treatment might help

improve HCV treatment outcomes for many patients drug use is uncontrolled. Factors shown to be related to the successful completion of HCV therapy include:

*“access to methadone maintenance treatment, close supervision by physicians specialised in both Hepatology and addiction medicine, and relative abstinence from alcohol” (Broers et al. 2005)(pp.327).*

These final points are part of an argument towards the promotion of more HCV specialist as discussed by Brown:

*“The most appropriate configuration for regional management of liver diseases including liver transplant services, hepatitis C services, paediatric Hepatology, and the most efficient use of resources that will avoid duplication and reduce waiting times should be devised. The volumes of service required suggest that transplantation should continue to be supraregionally funded in a limited number of centres but that liver centres may need to be more numerous because of the volume of patients requiring anti-viral therapy”*

(Brown 2002)(pp.626)

This opinion seems to have been taken into account by (The Hepatitis C Trust and The University of Southampton 2005), who make a series of recommendations of which point five (p4) suggests the introduction of “approximately 30 major centres for HCV

management with local networks linked into each of these centres in a hub and spoke arrangement” to create an appropriate infrastructure for diagnosis and treatment. Furthermore, an UK-wide survey recently concluded that significant variation exists in all aspects of the patient pathway, with staffing and funding of treatment as key barriers. It was recommended:

*“Services need to be expanded to form geographical clinical networks, and properly resourced to ensure greater uptake and more equitable delivery of services if the future burden of chronic liver disease is to be reduced”*

(Parkes, Roderick, Bennett-Lloyd, and Rosenberg 2006)

It seems that interest in geography and particularly the equitable geographical access of HCV specialist healthcare is rising amongst clinicians and policy makers. Recent evidence in France suggests that maybe patients with further to travel to seek primary healthcare consultations are less likely to be diagnosed (Monnet, Collin-Naudet, Bresson-Hadni, Minello, Di Martino, Carel, Jooste, Gagnaire, Evrard, Obert-Clerc, Miguet, and Hillon 2006; Monnet, Ramee, Minello, Jooste, Carel, and Di Martino 2008). On the current levels of specialist healthcare utilisation and treatment, Dillon writes (p.24):

*“Some compliance issues are related to drug toxicity... however, the majority are patient-centred. To ensure the maximum chance of success of therapy, it would appear*

*that patients need to take 80% of the dose for at least 80% of the time, which was intended at the initial commencement of treatment to achieve predicted success rates. Intuition and some reports would suggest the chances of achieving this may be increased by having a good support network for the patients in the form of easy access to experienced practitioners who can counsel the patient appropriately before commencing treatment and reinforce this counselling throughout treatment, offering advice and support on how to cope with the side-effects."*

(Dillon 2004)

Intuitively, patients with further to travel may not only have difficulty seeking primary healthcare attention, but engaging continuously with an HCV specialist centre frequently and over a long period of time, whilst coping with all the plethora of issues surrounding the infection. Those lacking mobility may not even be referred. Ensuring geographic access to healthcare may be of significance, if not vital, for the NHS is to tackle the HCV epidemic and associated liver complications in the future, yet no research has been conducted in this regard. The next chapter investigates literature in medical/health geography with special focus on geographic access to healthcare on all patient outcomes, in an attempt to tease out possible hypotheses for the HCV infected population.

# **3. Could HCV-related outcomes be influenced by geographic access to healthcare?**

## **3.1 Introduction**

The literature reviewed thus far has emphasised the significance of HCV infection in the realms of the biological and social. It is the aim of this chapter, and the thesis hereafter, to explore the spatial. More specifically, I discuss the extent to which health research has for a long time been focused, at least to a partial extent, on geographical inequalities of access to healthcare. The concept of geographic accessibility is defined; other factors that might interact with geographic access are discussed; evidence accumulated to date that investigates the extent to which geographic access might influence health outcomes per se is reviewed; and finishing off with the grounds for an enquiry as to the degree to which geographic access may be influencing outcomes related specifically to individuals infected with HCV in Scotland.



## 3.2 Background

'The Truly Disadvantaged' (1987) by William Julius Wilson, an American sociologist based at the University of Chicago, is widely cited for reinvigorating interest in the role that places (or 'neighbourhoods' as an alternative term commonly used) may have in defining people's life-chances (Dietz 2002; Ellen and Turner 1997; Friedrichs, Galster, and Musterd 2003; Sampson, Morenoff, and Gannon-Rowley 2002; Wilson 1987). Very briefly, Wilson's thesis contended that individuals who are exposed to residential concentrations of socioeconomic deprivation will be adversely affected by a lack of access to job information. In other words, it not only matters who one is, but where one also lives and who lives nearby, *sensu*, an effect of place.

This resurgence has been experienced in no uncertain terms within the field of medicine and health, developing areas of research now commonly branded as 'medical geography,' or more recently, 'health geography' (Kearns 1993; Kearns and Moon 2002). Now more than ever, the debate over whether it matters not only who you are, but where you are and what you have been, are currently, and will be exposed to in the future is being continuously discussed widely amongst numerous academics not only in geography but across disciplinary boundaries to epidemiology, sociology, economics, psychology and several others (see (Boyle 2004; Boyle, Curtis, Graham, and Moore 2004; Cromley and McLafferty 2002; Curtis and Rees Jones 1998; Diez Roux 2001; Diez Roux et al. 2001; Dorling, Smith, Noble, Wright, Burrows, Bradshaw, Joshi, Pattie, Mitchell, and

Green 2001; Ellen, Mijanovich, and Dillman 2001; Flowerdew, Manley, and Sabel 2008; Gatrell 2002; Gatrell and Loytonen 1998; Jones and Moon 1987; Kawachi and Berkman 2003; Kuh and Ben-Shlomo 2004; Macintyre, Ellaway, and Cummins 2002; McLafferty 2003; Pickett and Pearl 2001).

Interest in the “geographies of health,” a now widely-accepted phrase coined by Gatrell in the book of the same name (Gatrell 2002), particularly in terms of access to healthcare, predates Wilson as exemplified within references to Farr (Farr 1837, 1885), Durkheim (Durkheim 1897) and Black (Black, Morris, Smith, and Townsend 1988) that were discussed in the introductory chapter to this thesis. Another notable example and in this case one that is directly relevant to discussions of accessibility to resources, particularly healthcare, is Julian Tudor Hart’s classic thesis entitled “The Inverse Care Law” (1971). Tudor Hart argued that it was commonplace to observe that individuals living in areas of concentrated socioeconomic deprivation were less-well served by the NHS than the residents of comparatively wealthier places. Crucially, it was upon the understanding that poorer individuals were (and are still) more likely to need healthcare than those enjoying greater affluence, that prompted Tudor Hart to assert the geographical configuration of health services represented a spatial mismatch, or in other words, the famously-quoted “inverse care law” (Tudor Hart 1971).

However, like much of the literature on the potential influence of place characteristics on life chances in the last twenty years, the empirical evidence to support Tudor Hart’s

argument is thin on the ground and inconsistent (Dixon, Le Grand, Henderson, Murray, and Poteliakhoff 2003; Ellen and Turner 1997). Some studies have claimed to demonstrate that more deprived areas are poorly served by healthcare (Benzeval and Judge 1996; Furler, Harris, Chondros, Gawaine Powell Davies, Harris, and Young 2002; Gulliford 2002; Mercer and Watt 2007; Shi and Starfield 2001), though 'service' is not always in reference literally to geographic access but other dimensions of accessibility which are reviewed in a later section of this chapter. Many studies have found results counterintuitive to Tudor Hart's "law," with little social inequity in the geographic distribution of GPs found in some studies (Baker and Hann 2001; Barnett 1978; Guagliardo, Ronzio, Cheung, Chacko, and Joseph 2004) and another actually demonstrating higher rates of intervention amongst residents of socioeconomically deprived areas served by a nearby inner-city hospital (Black, Langham, and Petticrew 1995). As Field and Briggs (2001) note, primary healthcare is planned to provide care where it is needed (see also: (Jones and Moon 1987)): Tudor Hart was suggesting that in reality, the opposite distribution has manifested.

In recent studies, Macintyre and colleagues and other academics too, have published several works with findings to refute the "deprivation-amplification" hypothesis, reflective of the "inverse care law," of which it is contended that residents of more socioeconomically deprived areas tend to have less access not only to healthcare but also to other "health-promoting" facilities (such as green parks and shops offering fresh fruit and vegetables), but greater exposure to more "health-endangering" locations (e.g.

fast-food takeaways and garbage dumps) (Cummins and Macintyre 2006; Frumkin 2001; Maas, Verheij, Groenewegen, de Vries, and Spreeuwenberg 2006; Macdonald, Ellaway, and Macintyre 2009; Macintyre 2007; Macintyre, Macdonald, and Ellaway 2008a; Macintyre, Maciver, and Sooman 1993; Mitchell and Popham 2007; Mitchell and Popham 2008; Pearce, Witten, Hiscock, and Blakely 2007).

Although most studies so far in the UK have tended to find that the residents of more socioeconomically deprived places are generally not likely to suffer poorer levels of absolute geographic access (e.g. the minimum measured distance to the nearest GP, regardless of registration or utilisation) to healthcare and health-promoting resources (e.g. (Macdonald, Ellaway, and Macintyre 2009; Macintyre, Macdonald, and Ellaway 2008a)), this need not render further study of geographic accessibility a fruitless venture. Indeed, it had seemed intuitive for sometime before Tudor Hart and still to the author now that large geographical displacement, such as greater distance or journey time from one's residence to their desired location, will negatively influence the probability of interaction and, thus, the demand for a particular service (for more, see Christaller's concept of range (Christaller 1966). It is common sense that the absolute distance or journey time to healthcare may be interpreted as little more than an inconvenience by one person, but as a major challenge for another who perhaps lacks access to private transport. Geographic access is therefore in many ways a relative concept, and is actually fairly well recognised as a barrier to accessing primary and secondary

healthcare (see (Field and Briggs 2001; Haynes, Bentham, Lovett, and Gale 1999a), though surprisingly often overlooked (Goddard and Smith 2001).

The rest of this chapter is structured by the following. In the next section (3.3), I consider the meaning of geographic accessibility as used in recent literature and discuss some of the contrasting ideas and approaches. In section 3.4, I explore the extent of relativity of geographic access with reference to potentially interacting factors. The degree of evidence accumulated so far that supports or refutes hypotheses associating health outcomes with geographic access to healthcare are thematically reviewed in section 3.5. Upon gauging the extent of knowledge and scientific rigor of studies past, section 3.6 assesses the potential for application of geographic accessibility research to health outcomes related to individuals infected with HCV. Finally, section 3.7 concludes the chapter with clear hypothesis statements to which the rest of the thesis is dedicated to answering.

### **3.3 Geographic accessibility**

On the face of it, the idea of geographic accessibility appears simple. It is a reference to the displacement between oneself and where one would wish to go. Geographic access could be: the distance by which a person must traverse in order to view a property they

are interested in purchasing; or the time it would take to travel to the nearest supermarket to pick up groceries; or the total time of a return journey to consult a dentist or GP face to face. Is geographic accessibility, therefore, something knowable, measurable and absolute?

Probably not unlike most phenomena in the social sciences, geographic access is not so simple to define. Numerous studies have explored association between geographic access to healthcare through distance and travel-time (for example, see (Boyle, Kudlac, and Williams 1996a; Haynes, Pearce, and Barnett 2008; Lovett, Haynes, Sunnenberg, and Gale 2002; Martin, Wrigley, Barnett, and Roderick 2002; Nemet and Bailey 2000)) and health outcomes, of which the results are far from the consistent pattern that would be expected if the phenomena in question were indeed tame, measured and invariant across social groups.

Geographic accessibility is in fact a continuously evolving concept, which, in the context of healthcare, its meaning is too often assumed (Khan and Bhardwaj 1994). The greater the displacement between an individual and a service available at a particular location, it is generally thought, the lesser the demand for that respective service (Christaller 1966). However, it is quite reasonable to argue that geographic access to such a location (e.g. a GP practice) will vary from person to person, even if they neighbour each other on the same street (i.e., both individuals would, in theory, have the same displacement to traverse). One may be an adolescent, too young to drive a car and

dependent upon a bus or their parent for transport, whereas the other may be an individual of pensionable age and lacking mobility due to poor physical health. Each individual has contrasting challenges to overcome in order to visit the GP practice. The costs in terms of finances and time would be quite different, and it is possible that the service one individual might require could be available in alternative locations too if they were prepared to travel a little further (e.g. (Haynes, Lovett, and Sunnenberg 2003)), for what indeed might be perceived to be a more accommodating service for that person. In contrast, the other may have less potential choice maybe because the extra distance to enable it would be perceived to be excessive or not good value. Hence, social factors can play important roles in determining the nature of geographic access to healthcare, even when the absolute displacement between two individuals is held constant (Haynes 1987; Jones and Moon 1987; Joseph and Phillips 1984).

Such is life, and this complexity has been taken into account in the theorising of geographic accessibility. An important distinction is noted by Gulliford et al, who differentiate between an individual who has access, in that they may live quite close to a particular service they require, and an individual who has gained access, in reference to those who have actually utilised it (Gulliford, Figueroa-Munoz, Morgan, Hughes, Gibson, Beech, and Hudson 2002). This distinction is reminiscent of that Aday and colleagues argued earlier, in that there is a difference between what constitutes potential access, from actual access (Aday and Andersen 1974; Aday and Andersen 1981). Further,

sometimes the latter is referred to in alternative fashion as utilisation (Higgs 2004), and it is this term and that of potential that I adopt hereafter for sakes of clarity.

This distinction is possible, as Khan and Bhardwaj suggest, because geographic access is an outcome of a process (Khan and Bhardwaj 1994) and more than just a simple question of how far, or how long to get somewhere. A range of factors might influence the extent to which an individual with potential access to healthcare is able to convert that into utilisation (e.g. see Figure 8.1). Andersen and Newman (1973) attempted to devise a framework on accessibility that grouped some of these factors into so-called “predisposing”, “enabling” and “need” categories.

In brief, predisposing factors are referring to those that could describe the propensity of an individual to use a service, detailing characteristics such as age, gender, ethnicity, religion, and beliefs concerned with health and illness. Enabling factors, in contrast, describes the “means” or resources by which an individual is able to draw on to utilise the service, such as private transport or health insurance. Andersen and Newman suggest, though not strictly in these terms of reference, that any possible influences of place characteristics will also fall into this category (for instance, whether a person lives in a predominantly urban or rural area). Finally, there is need, which infers the perceived or medically evaluated reason for requiring the utilisation of a particular healthcare service (Andersen and Newman 1973).



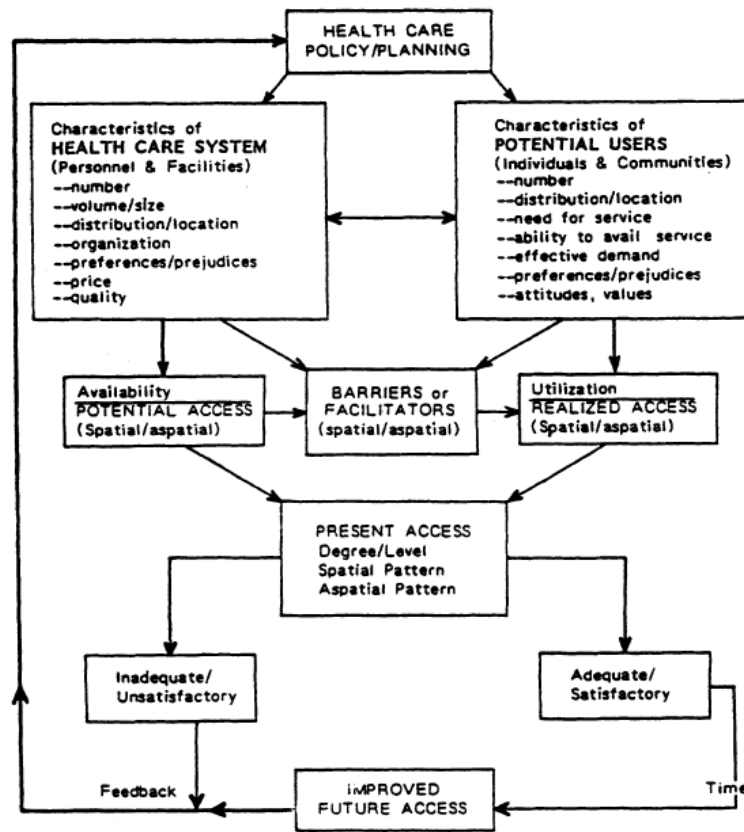


Figure 8.1: A schemata model of access to healthcare (Khan and Bhardwaj 1994)

Critiques of Andersen and Newman’s framework cite the challenge of quantifying variables and interrelationships (Joseph and Phillips 1984; Penchansky and Thomas 1981) and a lack of attention to changes over time (Field and Briggs 2001) (or, in more appropriate terminology for interested parties today, the changing exposure through the ‘lifecourse’ (Kuh and Ben-Shlomo 2004)). My own view is that through trying to include all possible factors into their framework, the potential importance of geography is somewhat diluted. Whilst Penchansky and Thomas’ “taxonomic definition of access [might be] one that disaggregates the broad and ambiguous concept into a set of

dimensions that can be given specific definitions and for which operational measures might be developed” (Penchansky and Thomas 1981)(p. 128), it does not necessarily solve any of the criticisms of Andersen and Newman’s framework. However, it is a useful classification to draw as, unlike Andersen and Newman, the geographical is explicitly modelled. It is these dimensions that provide structure to some of the discussion in this chapter.

Penchansky and Thomas compartmentalise the concept of accessibility into five interlinking, and arguably more manageable, dimensions (not least for recall since they all begin with the letter A): i) [geographic] accessibility; ii) availability; iii) affordability; iv) accommodation; and v) acceptability. Of course, it is the first dimension, geographic accessibility, which has been the main line of commentary for this chapter thus far and with good reason. For geographic accessibility to healthcare, as measured through such mainstay indicators as distance and travel-time between two points on a map, has been shown to be associated with various health-related outcomes, including: i) survival and cause-specific mortality (e.g. (Campbell, Elliott, Sharp, Ritchie, Cassidy, and Little 2000; Jones, Bentham, and Horwell 1999; Jones et al. 2008b; Kim, Gatrell, and Francis 2000)); ii) detection, diagnosis and delayed health-seeking behaviour (Bentham, Hinton, Haynes, Lovett, and Bestwick 1995; Monnet et al. 2006; Wang, McLafferty, Escamilla, and Luo 2008); iii) the variation of GP referrals to specialist centres (Boyle, Kudlac, and Williams 1996a; Grace, Abbey, Shnek, Irvine, Franche, and Stewart 2002; Grace, Gravely-Witte, Brual, Suskin, Higginson, Alter, and Stewart 2008; Jones 1987; Madeley, Evans, and Muir

1990); and iv) the utilisation of hospitals and specialist centres (Fortney, Rost, Zhang, and Warren 1999; Haynes, Lovett, and Sunnenberg 2003; Payne, Jarrett, and Jeffs 2000; Roderick, Clements, Stone, Martin, and Diamond 1999).

Before I turn to a thorough exploration of these studies and others with an eye towards finding application of theory in the context of HCV, the following section discusses literature on the remaining four dimensions of accessibility as defined by Penchansky and Thomas, of which I perceive as a set of factors that might interact with geographic accessibility to influence health outcomes.

### **3.4 Factors that might interact with geographic accessibility**

#### **3.4.1 Availability**

In the previous discussion of geographic access, the potential for choice was reflected upon. This is what Penchansky and Thomas referred to in an explicitly separate dimension entitled availability. Although more recent publications have seen fit to combine geographic accessibility with availability into a composite dimension of so-called 'spatial accessibility' (Guagliardo 2004; Luo and Wang 2003), hailing from the

similar types of measures used in analyses of job accessibility (Peng 1997) and the framework proposed by Aday and Newman (Figure 8.1), this remains an embryonic conceptualisation in geographies of health research. Little debate has ensued over what is gained and what is lost in terms of our potential understanding of the geographies of health and the extent to which geographic accessibility might have an influence upon health outcomes. To this end, I elect to keep the concept of availability separate, in view that notions of availability sensu Guagliardo, Luo and Wang, and Peng too seem to be absolute (and deterministic, as explained in the next chapter) whereas it feels quite reasonable that the range of locations from which one individual picks and chooses their services from is likely to vary in geographical extent from one person to another with different socioeconomic circumstances, attitude and behaviour.

So availability, as intuitive as it might sound, is a reference to the extent to which multiple service locations are present, offering some degree of choice to the individual. For instance, availability is the range of supermarkets in the area for grocery shopping, or the number of automatic teller machine (ATM) cashpoints located nearby from which to withdraw money, or the number of alternative locations where a person could consult a GP. Therefore, like geographic accessibility, availability is inherently geographical, but instead of referring to some sort of displacement, rather, it is a measure of how many different possibilities there could be for any given service.

But, equally importantly, availability may also be the degree to which a healthcare service has possession of the actual resources, equipment, technology, personnel and expertise that a patient might require. As Raine et al rather gravely suggest:

“A person cannot need health care if no intervention is available to improve their health. They may need health, but they do not need health care”

(Raine, Hutchings, and Black 2004)(p.228)

But the degree to which Raine and colleagues are correct depends very much upon scale. Not only geographical, but also temporal. For instance, a case in point is that of the recent patient from Scotland infected with the H1N1 (so-called “swine-flu”) virus, who was flown to Sweden (BBC News Online 2009) to utilise Extracorporeal Membrane Oxygenation (ECMO) technology. Briefly, ECMO is designed to circulate blood outside of the body during which it is oxygenated and then re-circulated back within the body. It is a modified heart-lung machine that provides better support for patients with severe respiratory or cardiac failure than other technology more widely available (Wolfson 2003). Crucially, why this is relevant is that ECMO technology is only available in one hospital in the UK (Glenfield Hospital, Leicester) and with a limited number of patients only able to use ECMO at any one time. If a patient in the UK requires ECMO, wherever they are, they are referred to the unit in Leicester. This means that geographic access to this particular form of healthcare varies extremely within the UK population, and with highly restricted availability in geographic terms.

However, when all the available spaces are assumed, as was the case of the aforementioned patient, healthcare was required but unavailable within the UK at that moment. Availability is a temporal construct. Potential access to ECMO had not changed, but its availability had, so unable to convert that potential into utilisation. The only option was, literally, to travel to expand the usual geographical coverage or scale to a different country in order to achieve availability. This illustrates quite well (albeit, on a quite extreme basis) how availability is not only subject to the geographical, but also the temporal. It also shows how the geographic extent of availability for the ECMO unit in Leicester is vast, but at certain times a person will have to travel much further to get the healthcare their condition requires. Although the cost of transportation to ECMO service is provided by the NHS, in other more common situations such as for patients requiring consultation with a GP or frequent specialist attention for haemodialysis or HCV combination therapy, availability is case-dependent and geographically and temporally relative.

Delving deeper into the geographies of health literature, Shannon has suggested that academics interested in geographic accessibility ought to reduce emphasis purely on displacement, in favour of re-imagining the ways in which spatial interactions occur (Shannon 1980). In short, Shannon was encouraging a focus on territory in a way that withdraws attention from the spatial configuration of healthcare, to more about where the individual is actually situated at different times. It is the idea that traditional measures of geographic access to healthcare (as will be discussed in the next chapter)

are actually surrogates for a wider web of relations between individuals and the places, or activity spaces, in which they live, work and play (Gesler 1992; Golledge and Stimson 1987; Patton 1975).

For example, it is highly conceivable (and I can personally attest) that an individual may perceive availability of a certain type of service, such as a dentist or a grocery store, to be the range of possible locations nearby their workplace, which may be quite some distance from their place of residence. Perceptions of healthcare availability may be no different. A recent study showed that only 56% of a population in Eastern England were registered with the GP practice located closest to their household (Haynes, Lovett, and Sunnenberg 2003). This might reflect ideas on activity spaces *sensu* Shannon and others, but with the study also demonstrating variation between individuals living in urban and rural areas (where persons in the latter were more likely to be registered with their nearest GP), the trend could also be driven by a geographic variation of health-seeking behaviour with individuals in more urban environments displaying a more consumerist approach to healthcare compared with persons in predominantly rural areas said to enjoy closer relationship with their nearest GP (Farmer, Iversen, Campbell, Guest, Chesson, Deans, and MacDonald 2006; Farmer, Lauder, Richards, and Sharkey 2003; Higgs 1999). The consumerist approach of city-based individuals may be driven by the generally shorter duration of GP consultations typical of more deprived urban areas (Furler et al. 2002; Mercer and Watt 2007; Stirling 2001), which could spur individuals to seek alternative opinion only a little further afield. Whereas the longer consultation

times and closer relationships enjoyed by persons in more rural areas, coupled by the probable limited supply of alternative locations may mean that the closest GP practice is more acceptable from this point of view. Acceptability, however, is another dimension that I turn to later in more detail.

Furthermore, in addition to the absoluteness of whether a service is or is not available within a particular distance or travel-time (or activity space) and open within a convenient timeframe for the individual in question (accommodation), availability is arguably dependent upon information and awareness. In an interesting reference to Tudor Hart, Mead and colleagues coined the term 'The Inverse Information Law' whereby those individuals with the greatest need for a specific type of healthcare were least likely to know about it (Mead, Varnam, Rogers, and Roland 2003). A recent study has also found a poor level of agreement between GIS-determined distances to green parks and respondents perceived distances (Macintyre, Macdonald, and Ellaway 2008b), which therefore suggests, like the distinction between potential geographic access and utilisation, the potential degree of availability may be quite different to the perceived range of options available to the individual (and hence, utilisation). As mentioned in the previous chapter, this lack of awareness of treatment and where to obtain it is certainly thought to be the case for many individuals infected with HCV, particularly those with a history of IDU (Davis, Rhodes, and Martin 2004; Davis and Rhodes 2004). They, who are often diagnosed with HCV but rarely treated, are described in the words of Edlin, as the "elephant in the living room" (Edlin 2004).



So, in discussion of availability, it seems that it too is a relative concept. Much depends upon where an individual lives and the spatial configuration of service locations surrounding them, but this does not necessarily reflect perceptions or knowledge of availability. Availability can vary through time and space and just because a person lives quite close to a GP practice (potential geographic access) does not always equivilise with the utilisation of that particular service location. Geographic accessibility and availability therefore, whilst obviously linked, cannot necessarily be grouped together in complete harmony as recent academics (Guagliardo 2004; Wang and Luo 2005) appear to suggest. And it is clear that other factors are important other than the range of service locations in determining whether an individual translates potential geographic access into utilisation. Following Penchansky and Thomas's lead, our discussion turns to the remaining three dimensions of affordability, accommodation, and acceptability.

### **3.4.2                      Affordability**

The third dimension, at its simplest, could pertain to whether a person is to be charged for the use of service they require. Moreover, it can also relate to whether an individual is prepared to accept those charges in receipt of the service. Some research has demonstrated the varying effect of user charges on the utilisation of healthcare between individuals of different socio-economic circumstances (Mossialos and Thomson

2003). One clear example is the choice of whether to use the NHS, or to have private health insurance. Evidently, there is a charge for the latter, and this becomes a more affordable option for the more affluent sector of society. Whilst this may not be particularly relevant in the UK context, where the majority of individuals utilise the NHS for healthcare, citizens of countries such as the US where a private system dominates has meant that approximately 45 million persons go without any insurance at all and millions more struggle to afford escalating healthcare bills, despite actually paying for insurance (Obama 2008).

Therefore, does the presence of an NHS in the UK guarantee affordable healthcare for all individuals in the UK? By international standards, the NHS is more equitable because of its reliance on general taxation rather than individual medical insurance sensu the US (World Health Organization 2000). But with respect to variation within the UK, the absence of charges and tax exemptions for low-income groups does not seem to create a fully 'level playing field' so to speak. Zero charge at the point of receiving a service does not include, for instance, the financial cost of literally travelling from home to a hospital, GP or any other healthcare location. The cost may be absolutely higher for those required to travel further, but relatively steeper for individuals on very low disposable incomes, even if living in close proximity to healthcare.

In the UK it is rare to measure income and various alternative measures, some as surrogates (e.g. benefit claims) but also in their own right (e.g. occupationally-derived

social class), are commonly used instead (Galobardes, Lynch, and Davey Smith 2007). For instance, studies of equity in healthcare for coronary heart disease (CHD) have found that although interventions tend to be common in more socioeconomically deprived places, the observed level does not match that expected (Ben-Shlomo and Chaturvedi 1995; Black, Langham, Coshall, and Parker 1996; Black, Langham, and Petticrew 1995; Goddard and Smith 2001; Payne and Saul 1997). In other words, there is an unmet need experienced by the more disadvantaged individuals in UK society. Numerous other studies have shown similar trends, where individuals occupying less-favourable socioeconomic positions are less likely to receive health checks for cardiovascular disease (Waller, Agass, Mant, Coulter, Fuller, and Jones 1990); less likely to be assessed as 'urgent' (Pell, Pell, Norrie, Ford, Cobbe, and Hart 2000); less likely to receive treatment for angina (Dong, Ben-Shlomo, Colhoun, and Chaturvedi 1998); less likely to attend rehabilitation following a heart attack (Melville, Packham, Brown, Weston, and Gray 1999; Pell, Pell, Morrison, Blatchford, and Dargie 1996); and less likely to receive statins, despite being at greater risk of heart disease (Reid 2002). This evidence of a socioeconomic gradient is a so-called 'fact' of geographies of health and health research more generally (Marmot 2001; Marmot 2005; Marmot and Wilkinson 2006; Wilkinson and Marmot 2003).

Socioeconomic position ("the socially derived economic factors that influence what positions individuals or groups hold within the multiple-stratified structure of a society" (Galobardes, Lynch, and Davey Smith 2007)) is associated with various stages of the

typical clinical pathway: screening/detection; referral; treatment utilisation; and overall chances of survival. In terms of detection, there is evidence that the level of success of screening programmes for some cancers is poor amongst less advantaged socioeconomic groups (Campbell, Ferrante, Gonzalez, Roetzheim, Pal, and Herold 2001; Gatrell, Garnett, Rigby, Maddocks, and Kirwan 1998; Ionescu, Carey, Tait, and Steele 1998). This could reduce the overall chances of survival for these individuals (e.g. (Campbell et al. 2000; Coleman et al. 2001)), who are less likely to be diagnosed at an early and more treatable stage, such is the case with many types of cancer (and, potentially HCV). Similarly less-favourable trends have been found with mammography (breast cancer screening) in the US for women on low-incomes and with no medical insurance (Adams, Florence, Thorpe, Becker, and Joski 2003; Barrett and Legg 2005), and in the UK amongst women living in rented accommodation in more socioeconomically deprived areas (Banks, Beral, Cameron, Hogg, Langley, Barnes, Bull, Reeves, English, and Taylor 2002; Sutton, Bickler, Sancho-Aldridge, and Saidi 1994).

Furthermore, once contact has been established (i.e. diagnosis), it may be that travelling frequently to access healthcare (i.e. not just a one off screening visit) imposes greater financial challenges, not only for the cost of travel, but the length of time taken that might need to be taken out of employment or arranging child-care, or even transporting an entire family if that is the more acceptable option. In more rural, remote areas of the UK where public transport may be less frequent, more expensive and with journey times longer as road speeds are slower, traversing more rugged topography and often of

poorer road quality, it is quite possible to perceive that long distances or journey times may discourage the utilisation of a free healthcare system. But even when controlling for geographic access, numerous studies have demonstrated variation in treatment by socioeconomic position (Campbell, Elliott, Sharp, Ritchie, Cassidy, and Little 2002; Carnon, Ssemwogerere, Wlamont, Hole, Amallon, George, and Gillis 1994; MacLeod, Finlayson, Pell, and Findlay 1999; Thomson, Hole, Twelves, Brewster, and Black 2001).

Thus, a free healthcare system does not necessarily make a universally affordable health service. Nor does a free to access NHS ensure favourable geographic accessibility, or a range of service locations available from which a patient is able to exercise choice (as is being promoted by the UK government, see (Appleby and Dixon 2004; Dixon and Le Grand 2006)). For those that can afford to do so, it is quite possible that individuals may elect to travel further, substituting convenience of proximity for greater benefits of choice (Haynes, Lovett, and Sunnenberg 2003). Such a decision may be made where more accommodating services are available at within an acceptable distance or journey-time, such as cheaper groceries or anonymous healthcare consultations. For individuals that cannot afford to travel further, perhaps geographic access to the nearest service location represents the only choice available. Therefore, in contrast to Guagliardo (2004) who by grouping geographic access and availability into a 'spatial accessibility' composite and by default brand affordability as aspatial, I would have to disagree and assert that even in the UK where there is universal healthcare, affordability is very much dependent upon where a person is. Moreover, as I have alluded to but now discuss in

greater detail, geographic accessibility, availability and affordability are all related to the final two dimensions of access as proposed by Penchansky and Thomas: accommodation and acceptability.

### **3.4.3 Accommodation and acceptability**

So far I have explored many of the factors documented within the literature that could interact to increase or decrease the likelihood that an individual would convert potential geographic access into the utilisation of the healthcare in times of need. Two dimensions remain to be discussed in detail, the first of which, accommodation, is very much a systemic dimension. On the other hand, acceptability might be interpreted as something rather more individualistic. An insight into the literature on each dimension will reveal the realistic possibility that closer is not always better.

Accommodation describes the extent to which services are structured to ideally facilitate patient utilisation, whereas acceptability might be the appreciation of this structure within an individual's own circumstance. An obvious example is the provision of interpreters in GP practices for some migrant workers who are less linguistically competent in the mainstream language of their host country (Jones and Gill 1998), or dedicated personnel for supporting persons that have difficulties of communicating or other impairments (Carter and Markham 2001; Ubido, Huntington, and Warburton

2002), helping to make healthcare more accommodating and acceptable. However, not every GP practice may be able to offer these services and, as previously suggested, sometimes individuals may need to forsake the convenience of proximity to increase the availability of more accommodating GP practices. Thus, it is conceivable that those individuals that can afford to do so may incur costs associated with travelling longer distances or journey times in order to expand the range of services available (Haynes, Lovett, and Sunnenberg 2003), hoping to find one that more acceptably meets the level of accommodation required. Evidently, for individuals living in more rural, remote locations and with restricted mobility, the increase in displacement to the next available GP practice or any other service location may be vast and the costs associated with its geographic access unaffordable and/or unacceptable.

Another clear example of accommodation is the opening hours of a GP practice, which might open during the evenings or at weekends to be more accommodating to those patients unable to attend otherwise. Time constraints imposed by employment contracts are an important factor for both making contact and then staying in contact with healthcare. For example, in a study of GP consultations by patients with asthma and diabetes, Field and Briggs showed healthcare-seeking behaviour was discouraged by employment-related time constraints (Field and Briggs 2001). Moreover, and in relation to the previous discussion of socioeconomic position and affordability, Field and Briggs found that employment-related time constraints were disproportionately suffered by those in manual occupations. Individuals in manual occupations, and more generally,

those in less-favourable occupationally-based social classes are widely recognised to have less autonomy and control in their work, find it more difficult to get time off, and are more likely to incur financial penalties for taking time off work due to the nature of the employment contract (often short-term, paid hourly) (Bartley and Plewis 1997; Rose 1998).

Therefore, an individual may have potential geographic access, but if taking time off work is perceived to be unacceptable and the availability of the nearest GP is only between the hours of 9-5, it is easy to see how in this situation a person might delay in arranging a consultation, or look to an alternative GP practice with opening hours more convenient to that individual within an acceptable distance or journey time. As has already been suggested, however, it is likely that the burden of poor health is disproportionately suffered by individuals in less favourable socioeconomic positions that sometimes actually make it more difficult to seek medical attention. For many, the idea of travelling further may be unacceptable in financial terms.

Accommodation and acceptability are also important when considering the doctor-patient relationship. It is thought to vary geographically, with GPs suggested to have closer relationships with their patients, and enjoying greater integration and visibility within rural, remote communities (Farmer et al. 2006; Farmer, Lauder, Richards, and Sharkey 2003; Higgs 1999). This may be a double-edged sword for the patient, who could have a more tailored service with a GP they may know reasonably well.



Conversely, individuals already diagnosed with a publically sensitive health condition, such as HIV or HCV, unfortunately stigmatised through association with IDU, may be uncomfortable with approaching their local GP for support and elect to consult elsewhere to maintain anonymity for fear of discrimination (e.g. (Zickmund, Ho, Masuda, Ippolito, and LaBrecque 2003)). In more remote areas where an individual must travel further to exercise choice, again, the ability to do so is likely to be the reserve of those that can afford to do so. For those not so affluent, this may result in the delay or complete withdrawal from seeking healthcare or maintenance of a treatment regimen (Chesney and Smith 1999; Hajela 1998; Hopwood and Southgate 2003).

There is a widely-known expression that goes: “following doctors orders.” Better known in medical literature as compliance, it has long been criticised for denoting obedience and conjuring negative imagery of noncompliant patients (Mullen 1997). In these terms, it is suggested that a patient that does not comply is in danger of being viewed as incompetent and unable to follow instructions, or even as deliberately self-sabotaging (Horne 2006). Again, this is also reflective of the HCV literature on attitudes within the medical profession towards persons with a history of IDU (Edlin 2002; Edlin 2004; Sylvestre, Litwin, Clements, and Gourevitch 2005). In the last ten years or so, there has been a sea-change in terminology, with the terms “adherence” and “concordance” also used. In contrast to compliance/obedience, adherence is “the extent to which the patient’s behaviour matches agreed recommendations from the prescriber” (Horne 2006), thus taking into account whether a patient agrees to commit to the doctor’s

regime. Furthermore, concordance is an idea “relating to the patient/prescriber relationship and the degree to which the prescription represents a shared decision” (Horne 2006), therefore implying a more equal distribution of power between GP and patient. All well and good, but to what extent has the intention of these new labels have been translated into reality? Are GPs perceived to be more accommodating of their patient’s views when making decisions over referral or treatment prescriptions, or are patients still expected to just “follow doctor’s orders”?

Some evidence demonstrates that some patients, typically those with more favourable socioeconomic circumstances, enjoy greater involvement in their GP’s decision-making. For instance, in terms of whether an individual is referred to a specialist, Evans showed those GPs who referred a lot tended to be more likely to accommodate their patient’s request for referral (Evans 1993). Armstrong found those patients willing to put pressure on their GPs in order to gain referral were more likely to be referred than those that left the decision completely to the GP (Armstrong, Fry, and Armstrong 1991). As Hirschman previously argued, the more vocal, articulate, confident, persistent and demanding patients often get better treatment (Hirschman 1970). It seems that more affluent individuals are better endowed for engaging a GP in decision-making. In comparison, such concordance may be unimaginable or unacceptable to those occupying less favourable socioeconomic positions, who more likely to hide the full extent of symptoms from GPs, more often attempt to self manage pain due to concerns of having previously overused health services, and even harbour negative opinions of

their own self-worth with regards to treatment and life expectancy (Gardner, Chapple, and Green 1999; Richards, Reid, and Watt 2002; Tod, Read, Lacey, and Abbott 2001). Moreover, recent studies have even shown evidence that many individuals who present later-stage colorectal and lung cancer at diagnosis are likely to have normalised their symptoms, even when severe, attributing them towards everyday aches and pains (Bain and Campbell 2000; Corner, Hopkinson, and Roffe 2006).

Ideally, GPs would be able to recognise all symptoms and make the correct decision every time for every patient. But in reality, some patients it seems may be less willing to take part in concordance with their GP, who may have to go to great lengths to encourage participation (Heath 2006). If there is a lack of communication due to a poor awareness on the part of the patient and/or the GP is unable (or unwilling) to accommodate and encourage, some information might be withheld whilst other parts might be misinterpreted, and inappropriate guidance awarded (Balsa and McGuire 2001). For instance, some findings have suggested that individuals in more rural areas experience greater delays between referral and treatment, especially if they are initially directed to a local, non-specialist hospital (Bain and Campbell 2000; Bain, Campbell, Ritchie, and Cassidy 2002). It is not known, however, to what degree these indirect referrals are the result of a lack of communication or awareness, or the outcome of sympathetic accommodation and cooperation, taking into account what a patient finds acceptable given the constraints on their situation.

So, accommodation is a lot more than just being open during evenings and weekends and acceptability is not only whether patient is content with the circumstance. Very generally, each dimension can be viewed in terms of i) when a patient first seeks healthcare; ii) further experience in healthcare once contact has been established. Accommodation and acceptability can alter healthcare-seeking behaviour, prompting some to look further afield, whereas discouraging participation and increasing the propensity for delaying behaviour amongst others who are subsequently at a greater risk of presenting a poorer level of health at diagnosis. Accommodation is partly about communication and the level of input a patient has in a GP's decision-making. For some, no input may be acceptable whereas others might demand greater involvement or alternative opinion, the latter of whom tending to occupy more favourable socioeconomic positions and seemingly get better healthcare for their persistence. Acceptability is about whether an individual perceives travelling long distances and travel-times to be worth the hassle (i.e. the pursuit for accommodation), or the willingness to continue attending treatment frequently over a sustained period of time. Thus, accommodation and acceptability are socially and geographically contextualised and will interact with other dimensions to influence whether an individual's potential geographic access to healthcare translates into utilisation when they need it.

### **3.4.4**

### **Conclusion**

This section has presented evidence for each of the dimensions of accessibility as proposed by Penchansky and Thomas, with emphasis on linkage back to geographic access to healthcare. So for what at first seems a fairly intuitive hypothesis, that is the sheer hassle of travelling a long way for a consultation that many will associate with bad news, it seems that geographic access to healthcare may actually be a proxy indicator for a much richer complexity of relationships between an individual and the place they live in (Nemet and Bailey 2000). Some might read this section and conclude that measures of distance or travel-time to the nearest healthcare provider may be insufficient when attempting to analyse geographic access, but as will become very clear in the next section, this is precisely the route taken by most researchers. Thus, in turning to review the state of evidence accumulated so far that measures the extent to which geographic access to healthcare is associated with health outcomes, I would argue that one should beware the limits of the variables used with regards to the multi-dimensionality of geographic accessibility and the potential confounding of other characteristics, most notably, those correlated with socioeconomic position.

## **3.5 The potential influence of geographic access on health outcomes**

### **3.5.1 Introduction**

Having discussed approaches to geographic accessibility and several sets of factors that interact and influence, the aim of this section of the review is to explore the degree to which effects on health outcomes have been reported. For convenience, this section is thematically structured into reviews on: i) survival and cause-specific mortality; ii) detection, diagnosis and delayed presentation; iii) referral to specialist healthcare; and iv) the utilisation of specialist healthcare and continued follow-up.

### **3.5.2 Survival and cause-specific mortality**

Perhaps the most intuitive of all ways in which geographic access to healthcare might have a significant influence upon health outcomes is in times of an emergency. When a person requires immediate medical attention, such as due to an allergic reaction, or having been in a road traffic accident, the time it takes to receive attention may make the difference between more and less favourable outcomes. For instance, Wei et al found the distance between patient residence and the hospital of admission predicted

mortality for those experiencing their first myocardial infarction in NHS Tayside, Scotland (Wei, Lang, Sullivan, Boyle, Wang, Pringle, and MacDonald 2008). In England, after controlling for socioeconomic position, longer travel-times to hospital were still found to significantly predict mortality from asthma (Jones and Bentham 1997; Jones, Bentham, and Horwell 1999), though no significant association was found with travel-time to the nearest GP. In contrast, Jones and Bentham found no significant association between health outcomes and ambulance journey times to reach and transport individuals to hospital who had been involved in road-traffic accidents (Jones and Bentham 1995).

But it is not just survival in emergency situations that geographic access to healthcare might be an important explanatory variable for survival. A study in the US suggested that between 10% to 20% of mortality due to prostate cancer was explained by a lack of access to healthcare (Jemal, Ward, Wu, Martin, McLaughlin, and Thun 2005). Of course, it is not literally the long distance or travel-time that is responsible for the mortality. The relationship is more subtle, with greater displacement between individuals and healthcare suggested to increase the chances of delayed health-seeking behaviour and later presentation of symptoms, at which point the ability for medical professionals to treat their patients may be severely compromised and in some cases, mortality the most likely outcome. Poorer levels of geographic access to healthcare might also influence access to treatment via referral, treatment adherence, etc. Hence, some studies have

used this as a basis for measuring the association between geographic access to healthcare and survival from chronic disease, particularly with types of cancer.

For instance, Campbell et al in Scotland demonstrated lower probabilities of stomach, breast and colorectal cancer detection prior to death and reduced chances of survival from prostate and lung cancers amongst individuals with poorer geographic access from a specialist cancer centre (Campbell et al. 2000). In the north of England, Jones et al showed individuals with breast and colorectal cancers living further from a GP were more likely to be detected at a later stage, whilst those with prostate cancer and with further to travel were at greater risk of death. Meanwhile, travel-time to hospitals and specialist cancer centres showed no significantly consistent associations with detection or survival (Jones et al. 2008b).

In the south of England, Kim et al investigated the odds of survival following surgery for cancer and associations with geographic access to specialist cancer centres. They found that although those with the furthest to travel fared the worst health outcomes, stronger effects were observed for actually where the person was treated and the socioeconomic deprivation of the place resided in (Kim, Gatrell, and Francis 2000). In Germany, Kleeberg showed individuals with cancer were at greater risk of death the further they lived from a specialist cancer centre (Kleeberg 2004). In New Zealand, Haynes et al demonstrated lower chances of survival from prostate cancer amongst men with poor geographic access to their nearest GP. In addition, survival from colorectal,



breast and prostate cancer was also less likely amongst individuals living further away from a specialist cancer centre (Haynes, Pearce, and Barnett 2008).

So, there is at least some research that finds geographic access to healthcare to be an important predictor of survival, not only in emergency situations, but from chronic disease too. As was suggested before, it is not the literal or absolute displacement that has a direct effect on mortality. Most probably, it is the differential influence that geographic access might have on certain types of individual and admittance to clinical pathways, such as diagnosis, referral for treatment and adherence to treatment itself. It seems reasonable to hypothesise that liver-related mortality amongst persons infected with HCV may follow similar patterns, but no study so far has followed-up this line of enquiry. However, before discussing this possible avenue for research further, it is important to consider in more detail why the risk of mortality from certain cancers and maybe HCV tends to be higher amongst populations with poorer geographic access to healthcare. To do this, we need to explore associations between geographic access to healthcare and detection, referral and treatment utilisation.

### **3.5.3 Detection, diagnosis and delayed presentation**

It is commonplace within the medical literature to use the word “diagnosis” when a patient learns of their infection or other health condition from a GP or other medical

worker. Although in the following literature this is no different, I am choosing to use the word “detection” as well. This is because whilst diagnosis is individualistic terminology, detection can be attributed to a population-level (or ecological) study. Whether an individual has been diagnosed with a health condition or not could be expressed as a simple binary variable. Whereas, in terms of detection, the response becomes the number of individuals diagnosed as the numerator, over a denominator accounting for an underlying prevalence of an infection or health condition (i.e. a detection rate). Using this terminology is crucial to distinguish between the individual and population level, drawing on a lesson from the seminal work ‘Sick Individuals and Sick Populations’ by Geoffrey Rose (Rose 2001):

*“a large number of people at a small risk may give rise to more cases of disease than the small number who are at high risk” (pp.431)*

A individual-level binary of diagnosed/not diagnosed of a particular cancer might tell us something about which characteristics are associated with becoming known to the medical profession. In contrast, the detection of the same cancer within populations at risk or in certain areas may vary from higher to lower than expected, and this may help to tell us something about the spatial clustering of certain risk factors and area-level variation in the success of screening programmes, which might be less obvious from an individual-level analysis. From a policy perspective, it may be that reducing a population-level risk factor slightly for a lot of people will save more lives in the long-

term than a focus upon a minority of individuals at high risk. This distinction is important to understand the extent to which geographic access might negatively influence the rate of detection of HCV, and is adopted throughout the remainder of the thesis.

According to the classic study by Zola, it is the 'natural state' of the individual to delay consulting a general practitioner (GP). Delays may be because of [but not limited to] – a lack of time or money, nobody to take care of dependents or other duties, feelings of guilt, shame, fear or embarrassment, a dislike of medical staff, needles or hospitals, or bad prior experiences of the medical system (Zola 1973). Therefore, it is highly probable that the gradual occurrence of symptoms for chronic conditions, such as cancer or HCV-related complications, may have emerged for some period of time before diagnosis is made (and could have been rationalised due to everyday causes, as previously inferred). Zola contended that individuals tend to seek medical care after prompts, or 'triggers,' which might include encouragement by a family member, or a sudden increase in severity of symptoms. The sheer hassle of having to travel relatively far for something associated with bad news is not the most attractive of combinations, and it is rather intuitive that academics have for a long time suggested that longer distances and journeys to healthcare are likely to encourage delays in seeking medical consultation (Farmer et al. 2006; Haynes, Bentham, Lovett, and Gale 1999b; Jones, Bentham, Harrison, Jarvis, Badminton, and Wareham 1998; Wellstood, Wilson, and Eyles 2006).

Numerous studies have shown associations between geographic access to both primary and secondary healthcare and rates of utilisation or inpatient episodes (Bentham and Haynes 1985; Field and Briggs 2001; Haynes, Bentham, Lovett, and Gale 1999a; Haynes and Bentham 1982; Jones et al. 1998; Nemet and Bailey 2000). The hassle of travelling long distances and journey times could especially influence health-seeking behaviour amongst population groups that tend to suffer poorer mobility, reduced access to transport and other enabling resources, including the rural elderly and single-parents, the homeless and other marginalised persons (Arcury, Gesler, Preisser, Sherman, Spencer, and Perin 2005; Arcury, Preisser, Gesler, and Powers 2005; Haynes, Bentham, Lovett, and Gale 1999a; Higgs 1999; Watt, Franks, and Sheldon 1994).

Poorer outcomes related to cancer as discussed in the previous section have been found amongst individuals lacking geographic access to healthcare. In other studies, poorer prognosis upon diagnosis is most often the case amongst individuals detected later into the course of the condition (Corner, Hopkinson, and Roffe 2006; Lamont, Symonds, Brodie, Nwabineli, and Gillis 1993; MacLeod, Ross, Twelves, George, Gillis, and Watt 2000). Many studies have subsequently investigated the association between geographic access and the risk of late presentation and rates of detection. In Georgia state USA, Liff et al demonstrated those individuals resident in rural areas tended to have more advanced cancers at the time of diagnosis compared to individuals in urban areas, with particular excess of non-localised prostate cancer amongst persons of black ethnicity in rural areas (Liff, Chow, and Greenberg 1991).

In the case of breast cancer screening in Illinois, Wang et al show individuals with poor geographic access were significantly more likely to be detected at a later stage of disease progression (Wang, McLafferty, Escamilla, and Luo 2008). In another US-based study, Casey et al showed that individuals resident in predominantly rural areas were significantly less likely to be receive particular health screening services (including mammograms, papanicolaou “pap” tests and proctosigmoidoscopy tests (for colon cancer)) within the nationally-recommended timeframe than those resident in urban areas (Casey, Thiede Call, and Klingner 2001). Other studies have also found that a lack of access to health care, both GPs and also mammography screening, to be strong predictors of late cancer detection (Jacobellis and Cutter 2002; Mullins 1999). In addition, a lack of transportation was also identified as an important factor leading to late detection and lower rates of mammography utilisation (Engelman, Hawley, Gazaway, Mosier, Ahluwalia, and Ellerbeck 2002; Lannin, Mathews, Mitchell, Swanson, Swanson, and Edwards 1998).

Most of these studies originate in the US, which with a society very much dependent upon private transportation, the findings may not be transferable to the UK context. However, similar studies have been conducted outside the US, especially in Western Europe. In an area of France, Launoy et al demonstrated individuals with colorectal cancer were less likely to be detected at an early stage, causing problems for treatment and bleaker prospects for overall survival (Launoy, Le Coutour, Gignoux, Pottier, and Dugleux 1992). In Scotland, Haiart et al found that uptake of mammography screening

for a mobile unit, theorised to reduce the challenge of geographic access, still found a 2.4% decrease in screening rates with every 10% increase in distance measured (Haiart, McKenzie, Henderson, Pollock, McQueen, Roberts, and Forrest 1990).

Where topography and poor infrastructure exacerbates the remoteness of some rural communities, delays in healthcare-seeking behaviour may be more common, whereby stoic attitudes towards health become social norms (Beard, Tomaska, Earnest, Summerhayes, and Morgan 2009). It may be that consulting a GP is not only dependent upon geographic access, perceptible symptoms and triggers, but the propensity for health-seeking behaviour may also be influenced by the relationships that people form with their GPs. In remote areas where access to healthcare is limited, people may have more personal relationships with their local GP, who may also hold a deeply embedded position within the social networks that make up the fabric of rural life (Farmer et al. 2006; Farmer, Lauder, Richards, and Sharkey 2003).

Studies of mental illness in rural areas have argued that worries over the perceptibly-low levels of privacy afforded by these social networks contribute to fears over confidentiality, discrimination and rejection (Barney, Griffiths, Jorm, and Christensen 2006; Fuller, Edwards, Procter, and Moss 2000; Hoyt, Conger, Valde, and Weihs 1997; Jorm 2000; Jorm, Medway, Christensen, Korten, Jacomb, and Rodgers 2000; Pescosolido, Gardner, and Lubell 1998; Rost, Smith, and Taylor 1993). Such worries may increase stoicism and delays in health-seeking behaviour in rural communities irrespective of

access to a GP, and could also lead to social isolation and psychological distress for persons not perceived to be abiding local 'norms,' such as those with poor psychological well-being or a history of IDU (Casey, Thiede Call, and Klingner 2001; Crisp, Gelder, Rix, Meltzer, and Rowlands 2000; Day, Conroy, Lowe, Page, and Dolan 2006; Farmer et al. 2006; Fox, Blank, Rovnyak, and Barnett 2001; Fuller, Edwards, Procter, and Moss 2000; Wellstood, Wilson, and Eyles 2006). For individuals living in more rural, remote areas where the nearest GP is likely to be the only choice within a certain geographic coverage (Haynes, Lovett, and Sunnenberg 2003), the lack of availability may result in higher rates of ambulatory care sensitive conditions (ACSCs), which are conditions reported through hospitalisation that ought to be identified and treated in primary care (more commonly referred to as avoidable hospitalisations). These have been shown to be higher in areas suggested to lack geographic access to GPs (Basu and Friedman 2001; Gulliford 2002; Parchman and Culler 1999), but it could also reflect inaccurate diagnosis on the part of less-well informed GPs.

In the context of HCV detection and geographic access to healthcare, surprisingly, only two studies have been conducted so far. Both were by the same research group in a small area of France (Monnet et al. 2006; Monnet et al. 2008). First, Monnet et al (2006) used poisson regression to model lower rates of HCV detection than expected in areas lacking geographic access to healthcare. Importantly, this study lacked sufficient adjustment for socioeconomic position, as we know from the previous chapter that the prevalence of HCV infection is strongly associated with socioeconomic deprivation due

to IDU. So it was difficult to know whether the distance-decay was real, or an artefact of the expected lower overall HCV prevalence of infection in more remote, rural areas. In an attempt to correct for this oversight, Monnet et al followed-up with a second study (2008) using a rather limited and coarse-scale ecological socioeconomic areal classification, again finding significantly lower rates of detection in less accessible areas. Despite the design flaws, these studies remain the only application of the geographic access to healthcare hypothesis to HCV detection.

In review, it seems that a lack of geographic access is associated with delayed presentation and lower rates of detection. However, the extent to which delays in healthcare-seeking behaviour are due to the hassle of travel or social norms of stoicism or feelings of isolation is still open for debate. As I infer, Monnet et al's studies are the only attempts to apply this hypothesis in the context of HCV, but for a lack of adjustment for prevalence it is just not clear whether geographic access is a barrier to detection or, simply, that HCV infection is rarer in more sparsely populated areas. However, as discussed previously, the lack of HCV detection is a significant problem in the UK but no similar study to Monnet et al's has been attempted. The common theme running through most studies of this genre is the statistically significant associations between lower rates of detection and late presentation of symptoms amongst individuals lacking poor geographic access to healthcare. Carefully designed, large-scale quantitative research is consistently able to inform of whether individuals with a lack of geographic access are more likely to receive late diagnosis than those with better



geographic access, or if lower rates of detection are associated with poor geographic access. It could well be that in the UK, and especially in sparsely populated regions such as areas of Scotland, poor geographic access to healthcare severely reduces the likelihood of being diagnosed with an early stage of HCV infection and the lack of studies of this potentially modifiable risk factor resembles a significant gap in the literature.

### **3.5.4 Referral to specialist healthcare**

The previous section dealt with situations when an individual might delay before electing to seek medical attention for an undiagnosed health condition and ways in which longer delays may be associated with poor geographic access to healthcare. But once an individual has been diagnosed with a health condition that requires specialist attention, what then? In this section, I walk a little further down the clinical pathway towards the potential influence of geographic access upon GP referral decisions for specialist healthcare.

Many healthcare systems such as those found in the US, the Netherlands and the UK have adopted a regulated system of admitting access to specialist healthcare (Davies and Elwyn 2006). This is the communication process of referral, made by GPs to more specialised colleagues. Referrals may be made, generally, for at least one of the following reasons: i) further investigation and/or diagnosis; ii) specialist treatment; and

iii) advice and reassurance for the patient and/or the GP (Coulter, Noone, and Goldacre 1989). The process is often just a telephone call or letter (Piterman and Koritsas 2005).

An important role of the referral process is the more appropriate management of scarce resources. GPs, traditionally cast in the UK as the 'gatekeepers' to the NHS (Cox 2006), become the managers and regulators, granting access to those judged to have sufficient need for specialist attention. Rates of referral are often viewed as key response measures in studies of GP practice variation (Armstrong, Fry, and Armstrong 1991; Coulter 1998; Fertig, Roland, King, and Moore 1993; Forrest 2003; O'Donnell 2000). Referral decisions are supposed to be of great importance as they tend to have significant weighting on the subsequent allocation of resources in healthcare (Carlsen, Aakvik, and Norheim 2008). This has led many to question the extent to which some referrals are necessary, whereas others may be deemed inappropriate, not least by policy makers who, according to Coulter (1998) and Roland (1992), have tended to view high levels of referral as inefficient (Coulter 1998; Roland 1992). So what rate of referral is appropriate?

In fact, as O'Donnell argues, there is little information available on what makes an appropriate referral (O'Donnell 2000), so it is difficult to define any appropriate rate. It is known, however, that rates of referral vary, but again, very little is known why (Carlsen, Aakvik, and Norheim 2008). Much of the literature that does attempt to tease

out explanatory factors is now dated and has produced inconsistent findings (O'Donnell 2000).

Research has suggested a range of factors that might cause variation in GP referral decisions, which can be broadly categorised into four groups: i) patient characteristics, such as sex, age, number of previous consultations, socioeconomic characteristics, expectations, beliefs, mobility, type of condition and the perceived seriousness of the condition (Hippisley-Cox, Hardy, Pringle, Fielding, Carlisle, and Chilvers 1997; Wilkin and Smith 1987a; Wilkin and Smith 1987b; Williams, Jackson, and Turbitt 1997); ii) practice characteristics, including size and geographical location (Christensen, Sorensen, and Mabeck 1989; Delnoij and Spreeuwenberg 1997; Jones 1987; Kerssens and Groenewegen 1990; Madeley, Evans, and Muir 1990); iii) GP characteristics, such as knowledge of particular health conditions and referral protocol, personality, relationships with patients, colleagues and specialists (Cummins, Jarman, and White 1981; Feeney, Noble, and Waller 2007; Newton, Hayes, and Hutchinson 1991; Piterman and Koritsas 2005; Reynolds, Chitnis, and Roland 1991; Vehviläinen, Kumpusalo, Voutilainen, and Takala 1996); and iv) 'structural factors', such as the degree of access to a specialist care and waiting lists (Noone, Goldacre, Coulter, and Seagroatt 1989; Roland and Morris 1988).

According to Piterman and Koritsas (2005), the content and quality of referral communication, telephone calls and letters, is recognised to vary substantially. It may

be hypothesised that awareness plays some role in this process. For instance, Dowie suggested that a GP's awareness of the chances that a patient's health condition could become life-threatening was an important factor in the decision to refer to a specialist (Dowie 1983). Similarly, Roland et al found that the GP's who perceived the seriousness of disease to be infrequent tended to refer fewer patients (Roland, Grimshaw, Grol, Shanks, Johnson, Russell, and Taylor 1997).

This variation may be played out geographically, because in areas where the prevalence of some infections like HCV is low, such as more remote, rural areas, the frequency upon which GPs will come across infected individuals will probably be sparse. Consequently, knowledge of a rare infection, its natural history, and appropriate and up to date guidelines on referral protocol may be low compared with GPs that frequently diagnose and consult individuals with rarer health conditions. Similar trends in awareness amongst GPs may also distance-decay the further from a specialist centre they are situated, assuming that specialists are generally located in areas of greatest demand for their services (usually city-hospitals). Greater knowledge of referral protocol and better links between GPs and specialists are forged through regular contact, often with the development of joint clinics (Keene 2006). For individuals diagnosed with a rare health condition that is rarer still amongst those living in more rural, remote areas with poorer geographic access to a specialist centre, the odds they will be referred on to a specialist may therefore be lower compared to another person living closer. In other words, a lack of GP awareness may contribute to delays in

patients being able to utilise specialist healthcare that their health might warrant (Bish, Ramirez, Burgess, and Hunter 2005).

But the probable variation of GP awareness is not the only possible causation of lower rates of referral from more remote areas. Consider a recent exchange in the British Medical Journal on the introduction of so-called “referral management centres” (Anonymous 2006; Davies and Elwyn 2006; Drife 2006; Greenhalgh 2006; Heath 2006; Keene 2006), presented in the recent health white thesis entitled ‘Our health, our care, our say: a new direction for community services’ (Department of Health 2006). An amusing response by Greenhalgh (Professor of Primary Healthcare at University College London) enquired: “Is this an April Fool? Editor – I thought a general practitioner was a referral management centre,” (Greenhalgh 2006) is an important point and should not trivialise a serious debate.

The referral process can be seen as a form of introduction. GPs listen to their patients recounting experiences of specialist services and accumulate knowledge of how these services are perceived by the people that use them. It is logical that there may be an element of fear in a patient being told that they need to see a specialist: fear of a serious diagnosis or of painful or embarrassing procedures. It has been noted that many GPs spend considerable time in “painstaking and careful negotiation[s]” in order to persuade their patients that their referral will be beneficial (Heath 2006). The more personal relationships individuals are said to experience with their local GP in more

remote, rural areas (Farmer et al. 2006; Higgs 1999) and the longer consultation times that seem to be afforded in more affluent areas (Furler et al. 2002; Mercer and Watt 2007) might facilitate such negotiation with knowledgeable GPs. Some research has suggested that a patient who pro-actively requests and puts pressure on a GP to refer them to a specialist is more likely to be successful than one that relies solely on the judgement of the GP alone (Armstrong, Fry, and Armstrong 1991; Evans 1993). In contrast, patients with lower expectations may be less demanding of referral to specialist centres, a characteristic suggested to be more common amongst those in rural areas (Bain and Campbell 2000).

Thus, more affluent and articulate individuals with favourable potential geographic access to a specialist and those consulting knowledgeable GPs may be more likely to be referred. In addition, GPs may also consider value judgements of whether to refer a patient who expresses reluctance. For instance, the case of an elderly person living alone, lacking social support and resources, lacking mobility and recently diagnosed with HCV. It is possible, though rarely heard of course, that a GP sharing a closer relationship with this patient might weigh up the long-term benefit of referring them for treatment that requires lots of trips to hospital, has less chance of success in older patients due to the accelerated progression of liver-related complications, and a high likelihood of serious side-effects. As Higgs suggests, we know little of whether GPs are more reluctant to refer patients with poor geographic access to a specialist centre (Higgs 2004). Equally, there is no study that explores whether older persons lacking access to a

specialist are less likely to be referred in the context of HCV, perhaps because of a reluctance by the patient or the GP themselves.

Few studies have tested such hypotheses either directly or indirectly, though those that have do tend to find distance-decay effects. For example, in England, Madeley et al found that patients living further from a hospital were less likely to be referred. Similarly, in Wales, Jones showed that the chances of referral to hospital was less likely amongst those patients with further to travel (Jones 1987). In showing that awareness of cancer genetic services amongst GPs in rural areas was poor, Iredale and colleagues also found that patients living in rural areas and needing this specialised form of healthcare were less likely to be referred. In addition, GP's perception that distance, journey time and accessibility by private and public transport could influence patient attendance was taken into account in their decision to refer (Iredale, Jones, Gray, and Deaville 2005). Also in Wales, Boyle et al demonstrated that patients over 60 years old were less likely to be referred for renal replacement therapy the further they lived from the specialist centre (Boyle, Kudlac, and Williams 1996a). In a study of referrals for cardiac rehabilitation in Canada, Grace et al showed that individuals residing long distances to the nearest specialist cardiac rehabilitation unit were significantly less likely to be referred (Grace et al. 2002; Grace et al. 2008).

So in summary, once an individual with a particular health condition is diagnosed is only the beginning of a journey they may need to take in order to get treatment. Part of this

journey is referral, which ideally should not be influenced by geography, but by whether a patient really needs treatment. However, variation does exist, and there are reasons why geographic access to healthcare may be influential, though empirical studies are relatively rare. In the context of HCV, SIGN guidelines state that all persons diagnosed with HCV ought to be referred to an HCV specialist centre. However, as discussed in the previous chapter, the actual number of referrals is low. Patient referral to HCV specialist healthcare has not been explored geographically and this represents a genuine gap in the literature, as many of the possible scenarios mentioned are relevant to the situation in Scotland.

### **3.5.5                      Utilisation of specialist healthcare**

So far, literature has been reviewed on associations between geographic access to healthcare and survival/mortality outcomes, detection rates, late diagnoses and delays in healthcare-seeking behaviour, and GP referral decisions. If a patient were to be diagnosed, and referred to specialist healthcare should they require it, would that mean geography was no longer an issue?

As with many questions, the answer can be both yes, and no. Yes, geographic access to healthcare could still play an important role, because for the most part an individual will still need to travel to the hospital or specialist centre. These visits may need to be quite



often, over a significant period of time, which could be expensive and difficult to sustain (Bentham and Haynes 1985; Joseph and Bantock 1982). This is the dominant view within the literature as demonstrated in the reviewed literature below. But as has been clear from the previous discussion, not everybody gets diagnosed, and not everybody diagnosed is referred. Patients at this stage of the clinical pathway are likely to be highly selected, many of whom might be better placed to cope with travelling long distances or journey times. Whereas those more likely to struggle with the commuting might not even get the chance, being diagnosed or referred at a stage of poor health that requires a very different sort of treatment (i.e. an organ transplant). Clearly, each scenario is realistic, but where does the weight of the evidence lie?

Even of the selected population that is referred to a specialist, some individuals will find it more difficult to travel than others. Elderly persons, single-parents, and individuals in less-favourable socioeconomic positions may be more vulnerable in this respect (Jordan, Roderick, Martin, and Barnett 2004; Nemet and Bailey 2000). In that case, association with geographic access and women attending a specialist centre for radiotherapy following breast-conserving surgery (BCS, a treatment for breast cancer) could be viewed as a study in which significant effects might be found. Postoperative radiotherapy is needed to reduce the odds that the cancer could reoccur, and is a location-specific treatment required several times a week for some time after surgery. In an early US-based study, Nattinger and colleagues found rates of BCS were higher in urban areas compared to those more rural. Moreover, rates were higher in teaching

hospitals (compared to non-teaching), larger hospitals (relative to small), and hospitals with on-site radiation and geriatric services, all of which suggests that more accommodating hospitals might retain a greater proportion of women needing radiotherapy (Nattinger et al. 1992).

In a more recent study of the same outcome variable but testing the effect of distance between residence and specialist, Nattinger and colleagues found the use of radiotherapy following BCS was less likely among women with the furthest to travel, especially for those aged over 65 (Nattinger, Kneusel, Hoffmann, and Gilligan 2001). Similar results were found by Athas and colleagues, who in also using a distance measure, found an inverse association between geographic access to a specialist and uptake of radiotherapy after adjusting for age (Athas, Adams-Cameron, Hunt, Amir-Fazli, and Key 2000).

In a study that explores the choice of having BCS or modified radical mastectomy (MRM) treatment for breast cancer, Meden and colleagues hypothesised that the latter may be more acceptable for women living further from a specialist due to the burden of travel for radiotherapy following BCS. In support of this hypothesis, their study found significant positive association between distance and MCM treatment instead of BCS (Meden, St. John-Larkin, Hermes, and Sommerschild 2002).

In Italy, utilisation rates of radiotherapy (not cancer-specific) decayed with increased distance from a specialist centre (Pagano, Di Cuonzo, Bona, Baldi, Gabriele, Ricardi,

Rotta, Bertetto, Appiano, and Merletti 2007), though this study was limited from ecological fallacy and the use of large areal units. In contrast, Jack and colleagues used a more complex statistical model to demonstrate geographic variation in treatment of patients with lung cancer, for which one explanation given was due to variation in access to specialist centres (Jack, Gulliford, Ferguson, and Moller 2003).

Also in England, Jones and colleagues explored the influence of travel-time on a range of cancer-specific hospital-based treatment. This study used a range of variables unavailable to most analyses, including information on tumour stage and pathology characteristics (both of which may influence the type of recommended treatment). Similar to the US studies of post-BCS radiotherapy, patients with the furthest to travel to a specialist centre were less likely to have received radiotherapy following treatment for cancer of the breast, colon, rectum, lung, ovary and prostate. Patients diagnosed with lung cancer were also less likely to receive surgery and those with lung or rectum cancer were also less likely to receive chemotherapy the further they lived from a specialist (Jones et al. 2008a).

In contrast to the distance (or travel-time) decay patterns found in the literature so far, Jones and colleagues also demonstrated the one example of a significant inverse trend. Patients diagnosed with cancer (breast, colorectal, bronchus, ovary and prostate) and resident over longer travel-times to a specialist centre were more likely to have utilised treatment relative to those living in closer proximity, after controlling for socioeconomic

deprivation. Crawford and colleagues suggested a possible explanation around the greater difficulty of providing healthcare in more deprived areas, which are typically located nearby specialist cancer centres (Crawford, Sauerzapf, Jones, Haynes, Zhao, and Forman 2007). Alternatively as I have already suggested, this may also be due to selection bias within the sample itself.

Also in England, Roderick and colleagues (Roderick et al. 1999) investigated whether geographic access was associated with acceptance onto renal replacement therapy (RRT) for haemodialysis. After controlling for numerous covariates including age, sex, ethnic group and socioeconomic deprivation, patients living further from a specialist centre were less likely to be accepted onto RRT.

The distance (or travel-time)-decay association has also been found in studies of cardiac rehabilitation (Ades, Waldmann, McCann, and Weaver 1992; Ades, Waldmann, Polk, and Coflesky 1992; Farley, Wade, and Birchmore 2003; Grace et al. 2002; Lieberman, Meana, and Stewart 1998), with stronger associations reported especially amongst older patients lacking geographic access to a specialist and those with limited access to a car (Harrison and Wardle 2005). Similarly for pulmonary rehabilitation (for treating respiratory disease), utilisation rates were lower amongst patients needing to make longer journey-times to a specialist after adjusting for covariates (Sabit, Griffiths, Watkins, Evans, Bolton, Shale, and Lewis 2008).

The majority of studies reviewed so far have shown directions of association that support the hypothesis of poorer geographic access associated with worse utilisation outcomes. These studies have been largely of persons with some form of cancer, renal failure, and heart or respiratory disease. In the context of HCV, all these findings are relevant, but it would also be useful to explore whether there are similar findings for individuals at particular risk of poor psychological well-being, such as those with a history of alcoholism, IDU or substance misuse more generally.

The evidence-base for these risk groups is very limited, as acknowledged by Beardsley and colleagues who attempted to rectify the gap with a study of geographic access and possible influence on utilisation of outpatient drug treatment. After adjusting for numerous covariates, a distance-decay association with attendance was found (Beardsley, Wish, Fitzelle, O'Grady, and Arria 2003). In a study of outpatient treatment for alcohol dependency, Fortney and colleagues demonstrated lower rates of attendance amongst patients living further from hospital, especially amongst the elderly and after taking into account other important factors such as marital status and the severity of illness (Fortney et al. 1995). On the utilisation of outpatient mental healthcare post-inpatient treatment for substance misuse, Schmitt and colleagues reported patients lacking geographic access to a specialist made fewer visits whilst 60% of those living over 25 miles away did not attend at all (Schmitt, Phibbs, and Piette 2003). Fortney and colleagues also explored association between geographic accessibility to a specialist and visits for depression treatment. In common with previous findings, the

results showed that the patients with the furthest to travel made a significantly lower number of visits and had less chance of receiving the minimum guided number of visits recommended compared with those living in closer proximity (Fortney, Rost, Zhang, and Warren 1999).

In summary, much of the research on geographic access to specialist healthcare and utilisation has explored trends amongst individuals diagnosed with cancer, with the majority finding the hypothesised association though with one notable exception. It seems that these trends are replicated amongst population groups that might suffer especially from reduced mobility, such as the elderly, and also those individuals with poor psychological well-being. With these groups amongst those diagnosed with HCV in Scotland, and with the limited specialist HCV centres available but frequent trips required for treatment, it is again surprising that no study has explored the potential effect of geographic accessibility on rates of utilisation for people infected with HCV.

### **3.5.6 Conclusion**

There is an over-used expression in the newsthesiss and academic journals in reference to the potential effect of where an individual lives on their life-chances: the so-called “postcode lottery” (e.g. (Boseley 2003; Cannell 2008; Elliott 2004; Hall 2006; Lyon, Cobbe, Bradley, and Grubb 2004). This is not exactly the case as people generally tend

to choose where they live, and this fact has led many academics interested in place-effects to increasingly think about the potential for selection bias. When considering geographic access to healthcare, for example, it may be that individuals explicitly take this into account when choosing where they would like to live.

Furthermore, theorists on access to healthcare including Aday, Newman, Andersen, Penchansky and Thomas, plus a long list of notable others, hardly attribute things to chance. In reality, there are reasons why some individuals are more likely to suffer poorer health than others and we know some of them. Likewise, there are many reasons why some individuals with cancer are diagnosed early, whereas others much later. Some get referred early, whereas others much later or not at all. Again, this is not down to chance, there are reasons why these trends manifest. Sarah McLafferty, a recognised practitioner of health geography and with particular interests in geographic accessibility has suggested:

*“we know little about how the spatial organisation of health services and treatments influences the outcomes of those treatments”.*

((McLafferty 2003) p. 34)

This review of the literature, in contrast to McLafferty's comment and more generally towards non-treatment related outcomes, would suggest that actually we have some good ideas on what might be happening, but there is a lack of research actually testing the potential influence of geographic access on health outcomes. The complex relationships between individual characteristics, the characteristics of the places in which people live and those of the healthcare providers available within their own individually acceptable catchment areas are all likely to play a role and, in all probability, a major reason for the lack of research is not a lack of endeavour, but a limited supply of good-quality data.

Even so, very basic research questions remain barely explored. A case in point are the rare studies to have investigated rates of referral and associations with geographic access to a specialist. For persons infected with HCV, are GPs more reluctant to refer those who live further away? Another, slightly better-researched area is on the utilisation of specialist healthcare, yet studies have been highly concentrated around only a few major diseases and are still relatively uncommon. Again, for persons infected with HCV, is long distance or journey-time a barrier to utilisation of specialist HCV centres?

The evidence-base for detection and delaying behaviour is larger, perhaps because of larger sample sizes (relative to the smaller numbers of persons referred and utilising specialist healthcare). Also larger is the number of studies exploring trends in survival,



which could be viewed as an approach to proxy very late-stage detection of some health conditions where other measures of severity are unavailable. Perhaps these types of study are more prevalent because they calculate potential geographic access to the nearest GP, not the actual GP where a patient was in fact diagnosed. Whilst this is not a major design issue, the discussion of factors that might influence geographic accessibility did make it rather clear that not every individual will visit the GP closest to their home. Until better data becomes available, these more sophisticated analyses will have to wait. However, in the meantime, it does seem surprising that with all the issues of poor detection of HCV in Scotland that no study so far has attempted to at least replicate the detection and survival-style studies that have been so popular in the context of cancer.

In conclusion, geographic access to healthcare and potential influences on health outcomes appears under-researched. In the context of individuals infected with HCV, especially in Scotland given the varied topography and remoteness of rural communities, where detection rates are poor, referral rates are unsatisfactory, and attendance records at specialist HCV centres are low, even the most basic question of whether these outcomes are associated with a lack of geographic access to healthcare remain unanswered.

## **3.6 Applications for the thesis**

### **3.6.1 Introduction**

In the literature review thus far, biological, clinical and social aspects of HCV infection have been reviewed. The absence of spatial or geographical enquiries was noted and accessibility to healthcare identified as a genuine avenue for further research. The purpose of this section is to lay out the theoretical model of how geographic access to healthcare might influence health outcomes related to HCV infection and hypotheses from which the rest of the thesis is dedicated to testing. The models are thematically structured, following that developed previously in the literature review: i) detection; ii) survival; iii) referral; and iv) utilisation of specialist healthcare.

### **3.6.2 Detection**

An estimated 130 million people are infected with the hepatitis C virus (HCV), which accounts for 27% of cirrhosis and 25% of hepatocellular carcinoma worldwide (Alter, 2007; Perz, Armstrong, Farrington, Hutin, & Bell, 2006). Intravenous drug use (IDU) has been the primary mode of HCV transmission in Western, Northern and Southern Europe since the introduction of routine screening of blood donors in the early 1990s, though

many patients have been infected iatrogenically and by other less-common pathways (Hutchinson, Roy, Wadd, Bird, Taylor, Anderson et al., 2006; Shepard, Finelli, & Alter, 2005). A shortfall in the number of people diagnosed, relative to the estimated prevalence of HCV-infection has been previously noted in the UK and particularly in Scotland (Health Protection Scotland, 2008; The Hepatitis C Trust and The University of Southampton, 2005). The consequences of this under-detection are profound. Undiagnosed people will not be referred for specialist consultation and treatment that could cure them. Allowing HCV to progress into older age undetected increases the likelihood of developing life-threatening complications that are harder and more expensive to treat (Perz & Alter, 2006). It has been suggested that three-quarters of all liver transplants in the UK within 20 years will be due to HCV, with the cost of treating HCV-related liver complications over the next 30 years estimated at £8 billion (The Hepatitis C Trust and The University of Southampton, 2005). Thus, it is imperative not only to prevent further infection, but to diagnose and treat those people that are currently infected before the development of liver-related complications.

Monnet et al. (2006; 2008), working in France where the number of people diagnosed is also less than the expected prevalence, have suggested that poor geographic access to primary healthcare may be one driver of this shortfall in detection. There are several hypotheses that could explain why HCV detection rates appear to be poorer amongst populations lacking geographic access to primary healthcare.

First, according to Zola, it is the 'natural state' of a person to delay consulting a general practitioner (GP). Delays may be because of [but not limited to] – a lack of time or money, nobody to take care of dependents or other duties, feelings of guilt, shame, fear or embarrassment, a dislike of medical staff, needles or hospitals, or bad prior experiences of the medical system (Zola, 1973). In areas where topography and poor infrastructure exacerbate the remoteness of some rural communities, it is plausible that longer journey times to access primary healthcare may encourage delays in seeking medical consultation (Farmer, Iversen, Campbell, Guest, Chesson, Deans et al., 2006). Some studies have shown lower rates of medical consultation and detection of some diseases amongst more remote populations (Bentham & Haynes, 1985; Field & Briggs, 2001; R. Haynes, Bentham, Lovett, & Gale, 1999; R. M. Haynes & Bentham, 1982; Jones, Bentham, Harrison, Jarvis, Badminton, & Wareham, 1998; Nemet & Bailey, 2000). The hassle of travelling long distances and journey times could especially influence health-seeking behaviour amongst population groups that tend to suffer poorer mobility, reduced access to transport and other enabling resources, including the rural elderly and single-parents, the homeless and other marginalised persons (Arcury, Gesler, Preisser, Sherman, Spencer, & Perin, 2005; Arcury, Preisser, Gesler, & Powers, 2005; R. Haynes et al., 1999; Higgs, 1999; Watt, Franks, & Sheldon, 1994).

Second, the largely asymptomatic nature of the initial (acute) stage of HCV infection often means that the infection is able to progress undiagnosed to the chronic stage (Bellentani, Miglioli, Bedogni, Croce, & Tiribelli, 2005; Mondelli, Cerino, & Cividini, 2005;

Shepard et al., 2005). The processes borne by the liver during chronic HCV infection are referred to as fibrosis, leading to cirrhosis and hepatocellular carcinoma on average 20-30 years later (Kiyosawa, Sodeyama, Tanaka, Gibo, Yoshizawa, Nakano et al., 1990; Kiyosawa, Umemura, Ichijo, Matsumoto, Yoshizawa, Gad et al., 2004; Ryder & Beckingham, 2001; Tong, El-Farra, Reikes, & Co, 1995). Symptoms can include debilitating fatigue, nausea, cognitive dysfunction and a reduced overall quality of life (Cordoba, Flavia, Jacas, Sauleda, Esteban, Vargas et al., 2003; Dunne & Quayle, 2002; Foster, Goldin, & Thomas, 1998; Gifford, O'Brien, Bammer, Banwell, & Stooove, 2003; Rodger, Jolley, Thompson, Lanigan, & Crofts, 1999; Spiegel, Younossi, Hays, Revicki, Robbins, & Kanwal, 2005). These symptoms can contribute to an elevated risk of depression, particularly in women and increasingly prevalent in older age (Golden, O'Dwyer, & Conroy, 2005). The risk of depression is also several times higher in patients with a history of IDU (Brienza, Stein, Chen, Gogineni, Sobota, Maksad et al., 2000; Brooner, King, Kidorf, Schmidt, & Bigelow, 1997; Callaly, Trauer, Munro, & Whelan, 2001; Mason, Kocsis, Melia, Khuri, Sweeney, Wells et al., 1998). For people suffering morbidity associated with chronic HCV infection, faced with long journeys to visit their GP, it is conceivable that the severity of these symptoms may compound mobility issues and exacerbate the effect of geographic remoteness on delays in health-seeking behaviour.

Third, consulting a GP is not only dependent upon access and perceptible symptoms, but the propensity for health-seeking behaviour may also be influenced by the

relationships that people form with their GPs over time. In remote areas where access to healthcare is limited, people may have more personal relationships with their local GP, who may also hold a deeply embedded position within the social networks that make up the fabric of rural life (Farmer et al., 2006; Farmer, Lauder, Richards, & Sharkey, 2003). Studies of mental illness in rural areas have argued that worries over the perceptibly-low levels of privacy afforded by these social networks contribute to fears over confidentiality, discrimination and rejection (Barney, Griffiths, Jorm, & Christensen, 2006; Fuller, Edwards, Procter, & Moss, 2000; Hoyt, Conger, Valde, & Weihs, 1997; Jorm, 2000; Jorm, Medway, Christensen, Korten, Jacomb, & Rodgers, 2000; Pescosolido, Gardner, & Lubell, 1998; Rost, Smith, & Taylor, 1993). Such worries may increase stoicism and delays in health-seeking behaviour in rural communities irrespective of access to a GP, whereas could also lead to social isolation and psychological distress for persons not perceived to be abiding local 'norms,' such as those with a history of IDU (Casey, Thiede Call, & Klingner, 2001; Crisp, Gelder, Rix, Meltzer, & Rowlands, 2000; Day, Conroy, Lowe, Page, & Dolan, 2006; Farmer et al., 2006; Fox, Blank, Rovnyak, & Barnett, 2001; Fuller et al., 2000; Wellstood, Wilson, & Eyles, 2006). Since depression and other mental illnesses are particularly common amongst people suffering chronic HCV infection, and with IDU being the most common mode of transmission, it is quite possible that the under-detection Monnet et al. found in more remote, rural areas could be due to influences outside of the sheer hassle of travelling long journey times.

Fourth, detection rates may appear to be lower in more remote areas not due to under-detection, but simply because the prevalence of HCV is much lower amongst rural communities compared to those in urban areas. Previous studies have suggested that the prevalence of IDU, a major risk factor for HCV infection, tends to concentrate amongst groups in lower socioeconomic positions (SEP) (Alter, Kruszon-Moran, Nainan, McQuillan, Gao, Moyer et al., 1999; Armstrong, Wasley, Simard, McQuillan, Kuhnert, & Alter, 2006) and within more socioeconomically deprived areas (Craine, Walker, Carnwath, & Klee, 2004; Edeh & Spalding, 2000; Hutchinson, Goldberg, King, Cameron, Shaw, Brown et al., 2004). In the case of Monnet et al. (2003), the absence of statistical control for the prevalence of HCV risk factors could mean that the distance-decay result found was an artefact. Monnet et al later attempted to rectify this problem, conducting a follow-up study of the same population (Monnet, Ramee, Minello, Jooste, Carel, & Di Martino, 2008) using a large-scale classification of geographic areas by 'socioeconomic and cultural context.' The classification grouped 74 'cantons' into 6 categories: i) Lower-income urban; ii) Upper-income urban; iii) Outer suburbs; iv) Industrial rural; v) Dynamic rural; and vi) Remote rural. However, without surveys on a representative sample in France on the variation of HCV prevalence with socioeconomic context and in the absence of individual measures of SEP and a validated index of socioeconomic deprivation for small-scale areas, it is unlikely that this measure was an appropriate surrogate marker for the prevalence of HCV risk factors. In the least, the large-scale typology will suffer from ecological fallacy (Schwartz, 1994) and is likely to simultaneously mask smaller 'pockets' of deprivation in more affluent areas (Haynes &

Gale, 2000) whilst exaggerating the prevalence of HCV risk factors in other areas. Thus, unfortunately, despite the results of Monnet et al. (2006) showing lower HCV detection rates amongst populations lacking geographic access to primary healthcare, without a reliable adjustment for prevalence, we remain none the wiser as to whether poor geographic access to primary healthcare is having a causal influence upon HCV detection as the aforementioned results are likely to be the products of selection bias.

In this thesis, we examine the association between HCV detection and geographic access to primary healthcare in Tayside, Scotland. This study considers whether travel-times to primary care are associated with detection rates, and whether such an effect is attenuated once small-scale measures of socioeconomic deprivation are accounted for. We also separately explore the impact of geographic remoteness on HCV detection by patient history of opiate substitution therapy (a surrogate marker of past IDU behaviour) for an extended consideration of possible selection effects.

### **3.6.3 Referral to an HCV specialist centre**

In the UK, the General Practitioner (GP) has commonly been described as the 'gatekeeper to the NHS' or the 'first medical contact' within the healthcare system (Cox 2006). It is usually through a GP referral that patients with demonstrable need are able to access more specialised healthcare, often situated in more centralised, city-based



locations. This is the case for patients infected with Hepatitis C (HCV) in Scotland, where the Scottish Intercollegiate Guidelines Network (SIGN)(Scottish Intercollegiate Guidelines Network 2006) state that “referral to specialist care should be considered for all patients with active HCV infection and not restricted to potential candidates for antiviral therapy.” Referral to an HCV specialist centre is important, as HCV infection can be treated effectively. Sustained virological responses (SVR) over 97% have been reported for patients treated at an early (acute) stage of infection (Jaeckel et al. 2001; Kamal et al. 2006a; Kamal et al. 2006b). Patients referred later (during the chronic stage of infection), SVRs tend to be lower at 42-52% for genotype 1 and 76-82% for genotypes 2 and 3 (Fried et al. 2002; Hadziyannis et al. 2004; Manns et al. 2001; Zeuzem et al. 2004). In addition to access to treatment, those referred to HCV specialist centres are also able to draw on medical staff for differential diagnosis, clinical management, an assessment of the stage of infection and advice on precautionary measures to avoid secondary infection (Brown 2002; Scottish Intercollegiate Guidelines Network 2006).

Recent reports have suggested that less than half of all patients diagnosed with HCV in the UK are referred to a specialist centre(Pareek, Wiselka, and Grant 2007; The Hepatitis C Trust and The University of Southampton 2005; The Scottish Government 2008) though few studies so far have explored why. Previous research has suggested that patients with a history of intravenous drug use (IDU) are commonly viewed as poor candidates for treatment, of whom may comprise 85-90% of the overall infected population (Hutchinson et al. 2006). Some reasons include: i) a concern over a lack of

adherence to proposed treatment; ii) the exacerbation of psychiatric diseases; iii) and reinfection (Bini, Brau, Currie, Shen, Anand, Hu, Jeffers, Ho, Johnson, and Schmidt 2005; Edlin 2002; Edlin 2004; Edlin et al. 2005; Hallinan, Byrne, Agho, and Dore 2007; Loftis, Matthews, and Hauser 2006; Soriano 2006; Stoové, Gifford, and Dore 2005; Sylvestre, Litwin, Clements, and Gourevitch 2005). A recent study showed that patients reporting current IDU were significantly less likely to be referred to an HCV specialist, whereas there was no statistical difference between individuals with past IDU and those reporting no injecting history (Stoové, Gifford, and Dore 2005). Consequently, GPs that know a particular patient's current IDU (or alcoholic) behaviour may recommend alternative healthcare initially to address these issues prior to referral to an HCV specialist centre (Wilson, Wallace, Currie, and Schofield).

However, a common finding of several recent studies in the UK, France and the US is that HCV-related knowledge amongst GPs is low (d'Souza et al. 2004; Ouzan, Cavailler, Hofliger, Mamino, Joly, and Tran 2003a; Ouzan, Hofliger, Cavailler, Mamino, and Tran 2003b; Rotily, Loubiere, Prudhomme, Portal, Tran, Hofliger, Valla, and Moatti 2002; Shehab, Sonnad, and Lok 2001). A lack of awareness amongst some GPs may exacerbate prejudice held towards patients with a history of IDU, who may be personally blamed for acquiring HCV, held liable for perpetuating the epidemic and perceived as irresponsible and unworthy of further treatment (Day, Ross, and Dolan 2003; Paterson, Backmund, Hirsch, and Yim 2007). Awareness amongst GPs varies, with some research having asserted that contact between groups under certain conditions

can reduce prejudice (Allport 1954; Pettigrew and Tropp 2006). A recent study found some support for this hypothesis in the context of HCV, with more favourable self-reported attitudes amongst health workers that spent greater time with patients with a history of IDU (Brener, von Hippel, and Kippax 2007). Thus, we might expect GPs who more frequently consult patients with a history of IDU, for instance in socioeconomically deprived, often inner city areas where prevalence tends to be higher,(Craine, Walker, Carnwath, and Klee 2004; Hutchinson et al. 2004) to have greater knowledge of HCV protocol and more likely to refer. In more remote locations where the prevalence of risk factors is lower, however, GPs having only occasional exposure to patients with HCV and/or with a history of IDU may be more likely to lack HCV-related knowledge and less likely to refer. This may be because of discriminatory attitudes towards patients with a history of IDU, but it could also be because they may lack the competence to interpret hepatitis antibody test results, or are unaware of the latest SIGN protocol (d'Souza et al. 2004; Hallinan, Byrne, Agho, and Dore 2007).

In other words, chances for referral may depend not only on who the characteristics of a patient, but also where that patient lives. To our knowledge, no study so far has explored whether referral to HCV specialist centres vary geographically. In this thesis, we investigate for social and spatial patterning of referral trends to a single HCV specialist centre located in NHS Tayside, Scotland. The research questions were therefore:

1. To what extent are HCV-diagnosed patients with further to travel to a specialist centre less likely to be referred?
2. To what extent is there evidence that some patients are less likely to be referred due to a history of IDU?

#### **3.6.4 Utilisation of an HCV specialist centre**

In Scotland, the majority of persons chronically infected with Hepatitis C (HCV) remain undiagnosed and many of those diagnosed fail to reach and stay within HCV specialist care services.(Parkes, Roderick, Bennett-Lloyd, and Rosenberg 2006; The Scottish Government 2008) According to the Hepatitis C Action Plan for Scotland,(The Scottish Government 2008) nearly 50% of newly diagnosed infected persons, referred to HCV specialist centres, do not attend their appointment. Referral to an HCV specialist centre gives patients the opportunity to consult medical staff on appropriate courses of treatment, a differential diagnosis, expert clinical management, an assessment of the stage of infection and advice on precautionary measures to avoid secondary infection.(Brown 2002; Scottish Intercollegiate Guidelines Network 2006) For the 50% of patients that do not attend their referral or follow-up appointments, it becomes increasingly difficult for medical staff and policy makers to prevent complications of chronic HCV infection, which is a leading cause of liver cirrhosis and hepatocellular

carcinoma worldwide.(Alter 2007; Perz and Alter 2006; Perz et al. 2006) Therefore, low rates of HCV specialist centre utilisation are a significant issue to address.

In order to improve rates of utilisation, policy makers need knowledge of what is causing the low uptake of referral, and for those patients that do attend their initial appointment, which factors are influencing continued follow-up. Gender could be important, with men reported to know more about HCV treatment than women,(Walley et al. 2005) but with women more likely to seek healthcare for HCV.(Gisbers van Wijk, van Vliet, and Kolk 1996; Temple-Smith, Stooze, Smith, O'Brien, Mitchell, Banwell, Bammer, Jolley, and Gifford 2007). Studies (Davis, Rhodes, and Martin 2004; Davis and Rhodes 2004; Fraenkel, McGraw, Wongcharatrawee, and Garcia-Tsao 2006; Munoz-Plaza, Strauss, Astone-Twerell, Jarlais, Gwadz, Hagan, Osborne, and Rosenblum 2008; Walley et al. 2005) have suggested that low awareness of HCV-related healthcare is an issue, particularly amongst patients with a history of intravenous drug use (IDU) of whom comprise a large proportion of the infected population in the UK (Hutchinson, Bird, and Goldberg 2005; Hutchinson et al. 2006), USA (Alter 2007; Armstrong et al. 2006) and Australia.(Shepard, Finelli, and Alter 2005). This may be partially influenced by a lack of HCV-related knowledge amongst GPs more generally (d'Souza et al. 2004; Ouzan et al. 2003a; Ouzan et al. 2003b; Rotily et al. 2002; Shehab, Sonnad, and Lok 2001) which means that whilst some patients are referred, the significance of attending the referral appointment is not being conveyed to all.

Awareness of HCV amongst medical professionals could vary geographically. GPs who more frequently consult patients with a history of IDU, for instance in socioeconomically deprived, often inner city areas where prevalence tends to be high,(Craine, Walker, Carnwath, and Klee 2004; Hutchinson et al. 2004) are also likely to have knowledge of HCV protocol to convey to the patient. In more remote, rural areas where the diagnosis of HCV is less common,(Monnet et al. 2006; Monnet et al. 2008) it may be that GPs are less competent at interpreting hepatitis antibody test results or are lack knowledge of the correct protocol to communicate to the patient.(d'Souza et al. 2004; Hallinan, Byrne, Agho, and Dore 2007) Therefore, attendance of the first appointment could vary geographically, with lower rates of utilisation among patients living in more rural, remote areas.

Even for those patients that do attend their first appointment, however, geography may continue to be significant. For instance, patients required to travel much further to visit a specialist centre on a frequent basis and over a long period of time may find it more difficult to do so, compared with those patients that live closer.(Bentham and Haynes 1985; Joseph and Bantock 1982) A lack of geographic access can particularly influence utilisation rates amongst persons with limited transport options (e.g. the elderly).(Nemet and Bailey 2000) Low utilisation rates have frequently been associated with patients required to travel long distances and travel-times specialist healthcare centres for cardiac rehabilitation,(Ades, Waldmann, McCann, and Weaver 1992; Ades, Waldmann, Polk, and Coflesky 1992; Farley, Wade, and Birchmore 2003; Grace et al.

2002; Lieberman, Meana, and Stewart 1998) pulmonary rehabilitation,(Sabit et al. 2008) alcoholism treatment aftercare,(Fortney et al. 1995) outpatient mental healthcare,(Schmitt, Phibbs, and Piette 2003) depression treatment,(Fortney, Rost, Zhang, and Warren 1999) outpatient drug treatment,(Beardsley et al. 2003) breast cancer treatment and aftercare,(Athas et al. 2000; Jones et al. 2008a; Meden, St. John-Larkin, Hermes, and Sommerschild 2002; Nattinger, Kneusel, Hoffmann, and Gilligan 2001) and veterans hospital use in the US.(Burgess and Defiore 1994; Mooney, Zwanziger, Phibbs, and Schmitt 2000) The commitment to making regular trips, the opportunity-cost of having to take time off work or finding help to look after dependents (Jordan, Roderick, Martin, and Barnett 2004; Nemet and Bailey 2000), and stoic attitudes towards seeking healthcare (especially for stigmatised infections, such as HCV) (Casey, Thiede Call, and Klingner 2001; Crisp et al. 2000; Day et al. 2006; Farmer et al. 2006; Fox, Blank, Rovnyak, and Barnett 2001; Fuller, Edwards, Procter, and Moss 2000; Wellstood, Wilson, and Eyles 2006) may all be amplified by living in remote, rural areas. So far, however, no similar study has been published for utilisation rates of HCV specialist centres.

Therefore, in the case of explaining what factors are associated with the low rates of utilisation of HCV specialist centres, it seems intuitive that patients with further to travel may be less likely to attend their first appointment, or if they do, will find it more difficult to keep up with subsequent appointments compared with patients that live closer to an HCV specialist centre. This chapter explores these hypotheses using data

available within NHS Tayside (Scotland), where patients are referred to a single HCV specialist centre located in the city of Dundee and the surrounding topography and infrastructure exacerbates the remoteness of rural communities.

### **3.6.5 Survival**

In the UK, but especially Scotland, trends in chronic liver disease-related mortality have significantly increased over recent decades (Bosetti et al. 2007; La Vecchia et al. 2000; Leon and McCambridge 2006; Leyland, Dundas, McLoone, and Boddy 2007). Worldwide, hepatocellular carcinoma (HCC) accounts for between 70-90% of primary liver cancers, with over half a million people being detected annually (Bosch, Ribes, Díaz, and Cléries 2004; Parkin, Bray, Ferlay, and Pisani 2001; Yu and Yuan 2004) and a 5-year survival of approximately 5% in most countries (El-Serag and Mason 2000). The hepatitis C virus (HCV) is a significant cause of HCC and cirrhosis (Giacosa and Hill 1996; Ince and Wands 1999; Perz and Alter 2006; Perz et al. 2006). Approximately 130 million people worldwide may have HCV infection (Alter 2007) and an estimated 50,000 live in Scotland alone, though by December 31<sup>st</sup> 2006 only 22,073 cases of the infection had been detected (Health Protection Scotland 2007). If a person infected with HCV goes undetected, cirrhosis may develop 20-30 years post-infection and HCC a decade later, increasing the risk of death from liver-related causes (Alberti, Chemello, and Benvegno



1999; Alter, Margolis, Krawczynski, Judson, Mares, Alexander, Hu, Miller, Gerber, Sampliner, and et al. 1992; El-Serag, Davila, Petersen, and McGlynn 2003; Poynard, Bedossa, and Opolon 1997).

HCV infection can be treated effectively with pegylated-interferon (PEG-IFN) and ribavirin, with studies demonstrating high sustained virological response (SVR) rates over 97% (Jaeckel et al. 2001; Kamal et al. 2006a; Kamal et al. 2006b) for acute infection. SVR rates are lower if patients are detected later into the course of the infection (the chronic stage), ranging from 42-52% for those infected with genotype 1, to 76-82% for genotypes 2 and 3 (Fried et al. 2002; Hadziyannis et al. 2004; Manns et al. 2001; Zeuzem et al. 2004). For patients that have already entered the late stages of the disease by the time they are detected, their treatment options are more limited to palliative care or a liver transplant. However, the UK has only 7 liver transplantation units, performing 600-700 transplantations a year and with around 200 patients on the waiting list at any one time (Prasad and Lodge 2001). Findings in a recent report, "The UK vs. Europe – Losing the Fight Against Hepatitis C", (The Hepatitis C Trust and The University of Southampton 2005) predicted a 500% increase in the future demand for liver transplants in the UK if the current detection shortfall is not addressed.

Studies that identify barriers to the early detection and treatment of people infected with HCV are crucial for the development of effective strategies aimed at minimising the coming wave of HCV-related liver disease. Recent studies in France have suggested that

poorer access to primary healthcare may limit the detection of HCV (Monnet et al. 2006; Monnet et al. 2008). One of the reasons why HCV detection may be poorer in smaller, rural communities is the practical difficulties of seeking medical consultation (overcoming long distances, dilapidated infrastructure, reduced access to transport (Jordan, Roderick, Martin, and Barnett 2004; Nemet and Bailey 2000)). Another is that HCV is commonly asymptomatic early on (Bellentani et al. 2000; Mondelli, Cerino, and Cividini 2005; Shepard, Finelli, and Alter 2005), making it very common for infection to progress undiagnosed from the acute to the chronic stage. Unless they are identified as at a high-risk, usually through current intravenous drug use (IDU), people may not be tested for HCV until recognisable symptoms are presented much later into the chronic stage of infection. Some of these symptoms include debilitating fatigue, cognitive dysfunction, depression and a reduced overall quality of life, particularly for patients with a history of IDU (Brienza, Stein, Chen, Gogineni, Sobota, Maksad, Hu, and Clarke 2000; Brooner, King, Kidorf, Schmidt, and Bigelow 1997; Callaly, Trauer, Munro, and Whelan 2001; Cordoba, Flavia, Jacas, Saulea, Esteban, Vargas, Esteban, and Guardia 2003; Dunne and Quayle 2002; Foster, Goldin, and Thomas 1998; Golden, O'Dwyer, and Conroy 2005; Mason, Kocsis, Melia, Khuri, Sweeney, Wells, Borg, Millman, and Kreek 1998; Rodger, Jolley, Thompson, Lanigan, and Crofts 1999; Spiegel, Younossi, Hays, Revicki, Robbins, and Kanwal 2005). Not only might these symptoms decrease a person's physical mobility in order to travel to medical consultations, but studies have also argued that because social networks in remote communities may be denser and knowledge is less private, patient fears over confidentiality, discrimination and rejection

may discourage health-seeking behaviour altogether (Barney, Griffiths, Jorm, and Christensen 2006; Casey, Thiede Call, and Klingner 2001; Crisp et al. 2000; Day et al. 2006; Farmer et al. 2006; Fox, Blank, Rovnyak, and Barnett 2001; Fuller, Edwards, Procter, and Moss 2000; Hoyt, Conger, Valde, and Weihs 1997; Jorm 2000; Jorm et al. 2000; Pescosolido, Gardner, and Lubell 1998; Rost, Smith, and Taylor 1993; Wellstood, Wilson, and Eyles 2006).

Education and awareness of HCV amongst health professionals is a key factor in the detection of HCV, but is thought to vary widely in the UK (The Hepatitis C Trust and The University of Southampton 2005) and may be spatially biased towards large city-based hospitals that house HCV specialist centres and hepatologists. Although every GP should be able to detect HCV, access to a hepatologist is significant for being able to provide specialist consultation for patients that have HCV, providing a differential diagnosis, access to treatment and counselling (Brown 2002). A recent study of HCC mortality in Europe and the US has also suggested that patients treated at specialist centres tend to have better survival outcomes, indicating better overall management (Capocaccia, Sant, Berrino, Simonetti, Santi, and Trevisani 2007). GPs working in more deprived areas and in close proximity to HCV specialist centres may have greater education and awareness of HCV due to more frequent contact with patients with a history of IDU (Craine, Walker, Carnwath, and Klee 2004; Edeh and Spalding 2000), perhaps through harm reduction programmes and the dispensation of opiate substitution therapy (OST) (Solberg, Burkhart, and Nilson 2002; Strang, Sheridan, Hunt,

Kerr, Gerada, and Pringle 2005; Taylor et al. 2000). As such, patients detected may stand a better chance of being referred on to the nearest HCV specialist centre. In contrast, poorer awareness amongst GPs in smaller rural communities may reduce the likelihood of recognising presented symptoms, and perpetuate the IDU and HCV-related stigma, with patients often assumed to be drug users, personally blamed for acquiring the disease, held liable for perpetuating the epidemic and perceived as irresponsible and unworthy of further treatment (Paterson, Backmund, Hirsch, and Yim 2007).

The practicalities of overcoming long distances, a lack of symptoms early infection, a tendency for more stoic attitudes towards seeking medical consultation, the exacerbation of remoteness for people suffering debilitating health, probable lower education and awareness of HCV amongst GPs and an increased risk of stigma and discrimination are all interlinking factors that may culminate in higher incidences of liver-related disease and poorer survival amongst HCV-infected populations lacking access to a specialist centre. In this thesis, trends in liver-related mortality amongst patients infected with HCV in Scotland and association with geographic access to healthcare and by the type of place in which diagnosis was received are investigated.

## **4. Data and methods**

### **4.1 Introduction**

The previous chapters have investigated the biological and social elements of research on HCV infection, highlighted gaps in knowledge with emphasis towards the possibility that geographic accessibility to healthcare could be influencing HCV-related outcomes, and reviewed the state of the evidence on geographic access. The purpose of this chapter is to utilise this knowledge with regards to developing the study in NHS Tayside. Here, the chapter begins by describing the geographical area of focus, the data available and how it was used, and the steps taken in order to estimate measures of geographic accessibility. With regards to study design and statistical approach, these details are discussed in the relevant analytical chapters.

### **4.2 Study Setting**

Scotland, the most northerly of the countries within the United Kingdom (UK), is surrounded by England to the south, the North Sea to the east, the North Channel and Irish Sea to the south west, and the Atlantic Ocean to the north and west. The

population geography of Scotland varies considerably (Figure 9.1) with the capital city of Edinburgh on the Firth of Forth, flanked to the west by Glasgow, the largest city in Scotland, and the heavily populated 'central belt' of towns and villages that flow inbetween. The Highlands, Fort William and Inverness to the north, St Andrews and Dundee in the east and Aberdeen to the north-east. Coldstream in the south, nearby the town of Berwick over the border in England. The Orkneys and Shetland Isles to the extreme north, the Hebrides to the most fartherly west.

It is a particular area of Scotland in which this study is set. The geographical region denoted by NHS Tayside, a 'healthboard', is one of fourteen in Scotland (Figure 9.2). NHS Tayside has responsibility for providing primary and secondary healthcare to the local community, through contracted services of 278 GPs, to the management of the three acute hospitals of Ninewells Hospital and Medical School, Perth Royal Infirmary, and Stracathro General Hospital (Steinke et al. 2002b).

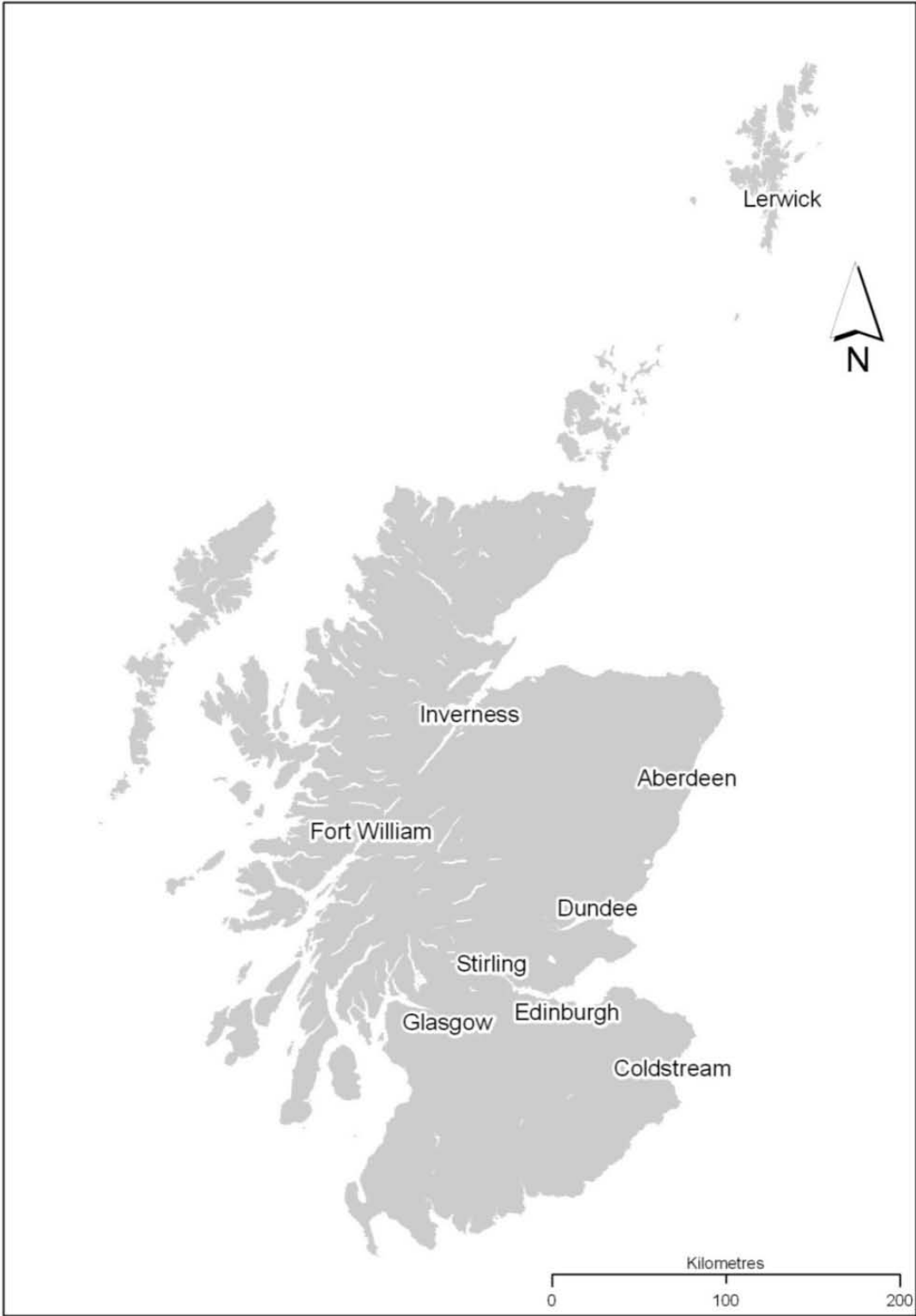
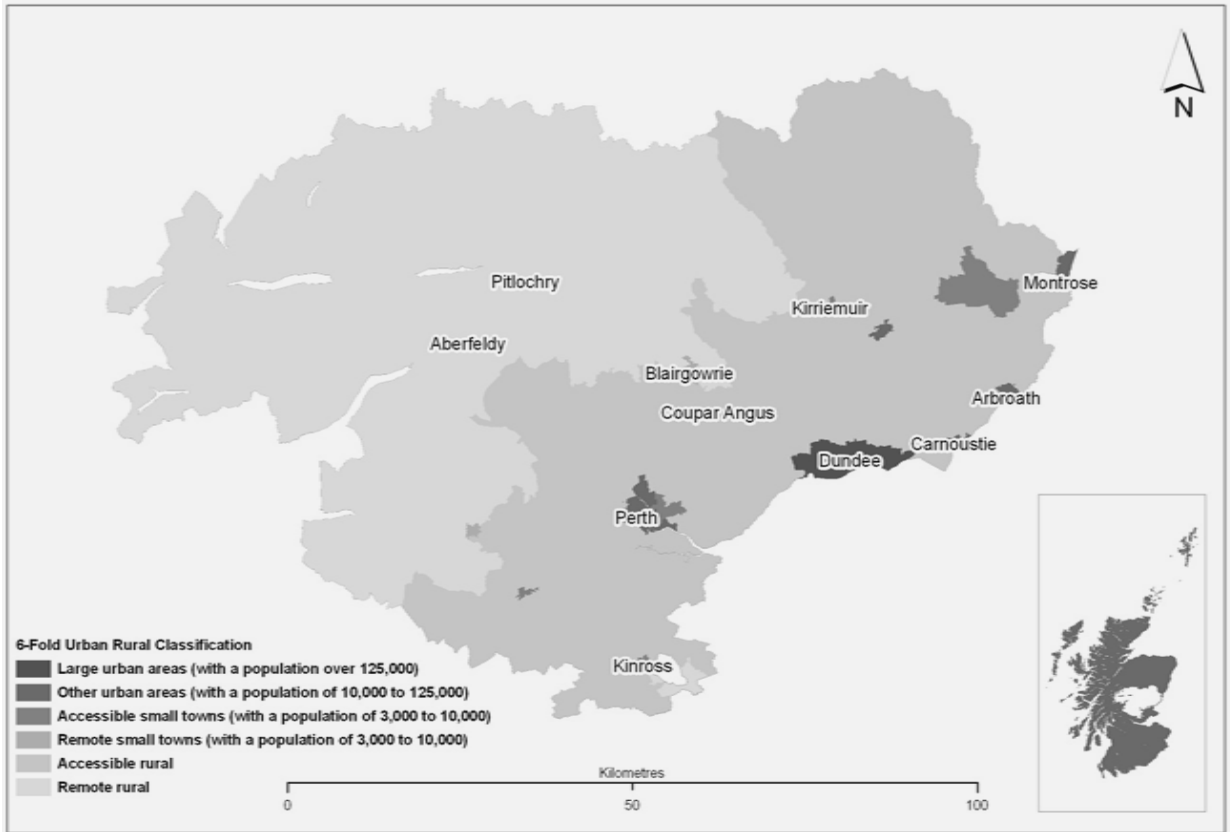


Figure 9.1: Scotland



Figure 9.2: Scotland's National Health Service healthboards





**Figure 9.3: The Scottish Executive 6-Fold Urban-Rural Classification: variation within NHS Tayside (location in Scotland inset)**

The population geography of NHS Tayside (Figure 9.3) ranges from the sparsely populated rural and remote areas of the north and west near around Loch Tay in the foothills of the Grampian mountains, the largest nearest settlements towns being Pitlochry and Aberfeldy, to the coastal towns of Montrose and Arbroath in the east and the largest settlements of Perth and Dundee to the south. Dundee, once known for ‘jute, jam and journalism,’ was once the centre of the global jute industry (Whatley 1992) though jam and journalism were less salubrious for local economy (McCarthy and Alan Pollock 1997). An overreliance upon jute, however, of which the profits had been enjoyed elsewhere, meant that when the industry declined in the early 20<sup>th</sup> century it

brought about the demise of the city and sent unemployment levels above 70% by the 1930s (Carstairs 1968).

Despite foreign investment in light manufacturing and textile industries during the mid 20<sup>th</sup> century, these have also subsequently disappeared due to competition abroad (Doherty 1992). Today, Dundee continues to struggle and currently has a level of unemployment, at 6.3%, higher than the average for Scotland (Scottish Economic Research 2009). More widely, the unemployment rate in NHS Tayside is at 4.4%, also higher than other parts of Scotland and the UK. The healthboard is characterised by a low rate of migration (Evans, McDevitt, and MacDonald 1995), with average earnings in 2001 only £299.25 per week which was 7.4% below the average for Scotland and 15.0% below that for the UK.

Both Edinburgh (Davies, Dominy, Peters, Bath, Burns, and Richardson 1995; Robertson, Ronald, Raab, Ross, and Parpia 1994) and Glasgow (Barnard, McKeganey, and Leyland 1993; Frischer, Bloor, Goldberg, Clark, Green, and McKeganey 1993; Frischer, Goldberg, Rahman, and Berney 1997) have been the focus of a lot of research on drug misuse, especially in the context of HCV infection (Goldberg et al. 2001a; Taylor et al. 2000; Taylor et al. 2008). Despite being smaller, however, the prevalence of IDU in Dundee has been estimated at 13.5/10,000 persons aged between 15 to 55 during 1990, which was suggested to be on par with levels observed in Glasgow (Hay and McKeganey 1996).

As was discussed in an earlier chapter, IDU is the major risk factor for the transmission of HCV since the early 1990s in Scotland. A recent study identified over 21,000 individuals in NHS Tayside with abnormal liver function (Steinke et al. 2002b), though only a small fraction of these patients have been examined for liver disease. A 2003 needs assessment estimated that the local population prevalence of HCV infection to be around 0.75%. This translates into about 3,375 individuals. However, only 1,235 antibody positive tests had been carried out, meaning that only 36.5% of individuals infected with HCV in NHS Tayside had been diagnosed (Tait and Dillon 2007). Moreover, only 1/3 of those diagnosed were referred to the HCV specialist centre based at Ninewells Hospital and Medical School in Dundee, with a fraction of these patients utilised their appointments. Only 100 patients were actually receiving treatment, 8.1% of those positively tested. This lack of testing and diagnosis, lack of referral to and utilisation of the HCV specialist centre denies individuals access to health promotion advice, harm reduction advice if relevant, immunisation and access to combination therapy (Tait and Dillon 2007). If no action is taken to improve these outcomes, the hypothesised wave of liver disease (Perz and Alter 2006) will materialise into high costs to NHS Tayside and the people that live there.

## **4.3 Patient records**

### **4.3.1 Introduction to datasets**

The data utilised in this thesis was drawn from various sources. Although patient records for individuals diagnosed with HCV infection were central, a lot of other data were also required to facilitate an exploration of the extent to which geographic access to healthcare influences HCV-related outcomes. This section gives an overview of the data and how it was used.

### **4.3.2 Epidemiology of Liver Disease in Tayside (ELDIT)**

Every patient registered with a GP in Scotland is allocated a unique 10 digit identification number, referred to as the 'Community Health Number', which is centrally held and continuously updated. In NHS Tayside, the Medicines Monitoring Unit (MEMO) has used fully-anonymised Community Health Numbers to link the records of primary and secondary healthcare data for patients with liver disease. This record-linkage database is called the Epidemiology of Liver Disease in Tayside (ELDIT) (Steinke et al. 2002a; Steinke et al. 2002b). Between 1991 and 2003, ELDIT held data on 1082 individuals positively diagnosed with HCV infection. Data on patient's sex, age at

diagnosis and 2001 Output Area of residence was also held. Linked to these records is data pertaining to i) virology; ii) prescriptions; iii) morbidity; iv) mortality; v) endoscopy; vi) biochemistry; vii) pathology; and viii) immunology. Those databases relevant for the thesis are outlined below. The ELDIT (and following datasets outlined) were accessed after gaining ethical approval from the University of St Andrews and the Central Office for Research Ethics Committees (COREC).

#### **4.3.2.1        *Virology***

Virology is the scientific study of viruses and the diseases that they cause. Computerised patient records exist for all requests for viral serology from primary and secondary healthcare for the hepatitis viruses in NHS Tayside since 1980. ELISA tests are have been used in regional viral laboratories to identify viral hepatitis. Only anti-body positive HCV diagnoses are held on ELDIT.

#### **4.3.2.2        *Prescriptions***

Since January 1993, MEMO has held patient-specific data on over 10 million dispensed prescriptions. These prescriptions include 'opiate substitution therapy' (OST) consisting

of methadone and buprenorphine, used in the rehabilitation of people addicted to heroin, which can be both prescribed and dispensed by GPs, private doctors and specialist centres in the UK (Solberg, Burkhart, and Nilson 2002).

#### **4.3.2.3      *Death registry***

All deaths since 1989 in NHS Tayside are electronically recorded through a copy of the General Registers Office-Death Certificate Database, with those relevant to patients diagnosed with HCV also held by MEMO and linked to ELDIT. The date and the underlying and contributing causes of death were included, with causes of death classified according to the International Classification of Diseases (ICD) 9th and 10th revisions, corresponding to years 1980–1999 and 2000–2005, respectively.

#### **4.3.3      **Hepatitis C Diagnoses Database****

The ELDIT is unique in Scotland for the extent of data-linkage on patients with liver disease, particularly on HCV infection. However, appreciating the significance of the HCV epidemic as a major public health issue (Hutchinson et al. 2006), Health Protection Scotland (HPS) devised a national database drawing data on all anti-body positive HCV

diagnoses in Scotland (Shaw, Taylor, Roy, Cameron, Burns, Molyneaux, McIntyre, Codere, and Goldberg 2003). Like ELDIT, these records come from testing laboratories dating back to 1991 and do not include anti-body negative tests. Between 1991 and December 31<sup>st</sup> 2006, 22073 individuals positively diagnosed with HCV infection were in the dataset (Health Protection Scotland 2007). The database contains data on sex, age at diagnosis self-disclosed history of IDU, the postcode unit of the location diagnosed and classified type (e.g. GP, hospital), the postcode district of residence, and the date and cause of death where relevant (McDonald, Hutchinson, Bird, Robertson, Mills, Dillon, and Goldberg 2008; Palmateer, Hutchinson, McLeod, Codere, and Goldberg 2007). This database was accessed through application to Dr Sharon Hutchinson, Senior Epidemiologist at Health Protection Scotland.

#### **4.3.4 NHS Tayside HCV Clinical Database**

Records of all patients referred to the HCV specialist centre at Ninewells Hospital and Medical School in Dundee are stored onsite in a database. Unlike ELDIT, this database does not include data on patients that were positively diagnosed, but not referred. Further, data available spanned the period 1991 to 2006 (n=658), three years more than ELDIT. Again, data on patient's sex, age at diagnosis, self-disclosed history of IDU and the 2001 Output Area of residence were all included. Furthermore, data was also

available reporting patient attendance and follow-up status. This database was accessed through Dr John Dillon, Consultant Hepatologist and Gastroenterologist (and supervisor).

### **4.3.5 Study sample definition**

It is common that datasets do not come precisely specified in a way that is conducive to instantaneous analysis. In this section, the derivation of study samples from those datasets previously outlined is now discussed.

#### **4.3.5.1 *Individuals diagnosed with HCV infection in NHS Tayside***

Of the 1082 patients available in ELDIT, many did not have complete information for every variable required. Table 9.1 displays the extent of the missing data, with 36 patients having no indication of sex and a further 10 with no Output Area of residence. These 46 patients were omitted from the analyses, as were patients that received diagnosis in prison (n=25) and those diagnosed before their 15<sup>th</sup> birthday (n=37, infected through vertical transmission) as geographic access to healthcare would not have had an influence upon detection. Moreover, those patients living outside of NHS Tayside



were also omitted from the overall study sample as similar patient record data from the surrounding healthboards of NHS Grampian and NHS Fife were not available.

	#obs
<b>Total original detected cases</b>	<b>1082</b>
<b>Variable</b>	<b>#Deleted</b>
no sex	36
no Output Area	10
in prison	25
age below 15	37
not a Tayside Output Area	84
<b>Total not used</b>	<b>192</b>
<b>Total sample</b>	890
	(176 deaths)

**Table 9.1: ELDIT – sample derivation**

Age group	Sex		Total
	<i>Women</i>	<i>Men</i>	
15-24	34	76	<b>110</b>
25-29	55	126	<b>181</b>
30-34	49	154	<b>203</b>
35-39	45	112	<b>157</b>
40 +	70	169	<b>239</b>
<b>Total</b>	<b>253</b>	<b>637</b>	<b>890</b>

**Table 9.2: ELDIT – sample by sex and age-group**

In total, 192 patients were omitted from the ELDIT database leaving 890 remaining, of whom 176 were reported to have died at some point during the time period 1991-2003. By way of summary, Table 9.2 shows the age-sex breakdown of the remaining study sample, with the vast majority of patients being male and under 40 years old.

#### **4.3.5.2      *Patients referred to the HCV specialist centre at Ninewells Hospital***

To ascertain whether patients that had been positively diagnosed with HCV were referred or not, the ELDIT-derived study sample needed to be linked to the NHS Tayside HCV Clinical Database. This procedure had to be operationalised by the author as both datasets are separate. Linkage was not straightforward as the Community Health Number was not present in the latter. Prior to linkage some cleaning of the data was required. First, since the clinical data contained records for patients diagnosed between 2004 and 2006, who would not have been in the ELDIT, these patients were omitted from linkage (n=123). Second, patients that had no date of birth or sex reported (the variables upon which linkage was based) were omitted (n=5), leaving 530 patients.

Linking records in both datasets by a combined sex-date of birth variable yielded 369 matched patients in both ELDIT and the clinical database. 17 records were duplicated due to identical sex and date of birth matches. In order to match patient records as accurately as possible, the first resolve was to match further by Output Area of

residence, which resulted in 10 clarified records. The second resolve was to match by the recorded date of diagnosis +/- one year (accounting for any possible lag or inaccuracy in reporting), resulting in a further 6 clarified records. One patient record was duplicated twice for which no further resolve was possible, so the three records were omitted, leaving an overall linked sample of 350 (referred) patients. Table 9.3 displays the age-sex breakdown of the ELDIT-derived sample and those that were linked to records in the clinical data (the 'referred' sample).

<b>Women</b>			
<b>Age Group</b>	<b>Diagnosed Patients</b>	<b>Referred Patients</b>	<b>% Referred</b>
15-24	34	19	55.9
25-29	55	27	49.1
30-34	49	25	51.0
35-39	45	20	44.4
40 +	70	22	31.4
<b>Total</b>	<b>253</b>	<b>113</b>	<b>44.7</b>
<b>Men</b>			
<b>Age Group</b>	<b>Diagnosed Patients</b>	<b>Referred Patients</b>	<b>% Referred</b>
15-24	76	27	35.5
25-29	126	41	32.5
30-34	154	58	37.7
35-39	112	54	48.2
40 +	169	57	33.7
<b>Total</b>	<b>637</b>	<b>237</b>	<b>37.2</b>

**Table 9.3: ELDIT – Clinical data – linked sample by sex and age-group**

#### **4.3.5.3 Referred patients utilisation of the HCV specialist centre**

For this study sample, patient records were required only of those that had been referred to the specialist centre. As ELDIT was not required, the full NHS Tayside Clinical Database from 1991 to 2006 could be used (N=658), albeit with some records omitted. Omitted records were due to not having an Output Area of residence (n=4), living outside NHS Tayside (n=38), no indication of sex (n=6), no date of diagnosis (n=78), were younger than 15 years old (n=4), were diagnosed in prison (n=29), or had unknown IDU status (n=32). This resulted in a total of 191 omitted records, leaving 467 patients available to analyse. Table 9.4 illustrates the derived study sample by sex and age-group.

<b>Age Group</b>	<b>Women</b>	<b>Men</b>	<b>Total</b>
15-24	27	41	68
25-29	33	65	98
30-34	31	71	102
35-39	22	60	82
40 +	37	80	117
<b>Total</b>	<b>150</b>	<b>317</b>	<b>467</b>

**Table 9.4: Clinical data – derived sample by sex and age-group**

#### **4.3.5.4 Patients diagnosed by type of healthcare provider**

In contrast to ELDIT and the NHS Tayside HCV Clinical Database, the HPS HCV Diagnoses Database only contains relatively coarse geographical information pertaining to the patients residences (postcode districts). Furthermore, in excess of 8000 patient records were missing this geographical data and with significant variation by healthboard, rendering its use in analyses unreliable. However, the focus was turned to where the patient was diagnosed, for which postcode unit data was available with less missing records, to identify the type of healthcare providing diagnosis. Of 22,073 patient records, 236 were missing an indication of sex, 281 missing a date of birth, 99 were under the age of 15, 275 locations were missing a unit postcode and 6853 patients were recorded as being diagnosed in prison or other non-classifiable locations. Thus, the total sample population available for study was 14,329, the age-sex breakdown of which is given in Table 9.5.

<b>Age Group</b>	<b>Women</b>	<b>Men</b>	<b>Total</b>
15-24	1123	1270	2393
25-29	1153	1971	3124
30-34	1038	1999	3037
35-39	699	1556	2255
40 +	1095	2425	3520
<b>Total</b>	<b>5108</b>	<b>9221</b>	<b>14329</b>

**Table 9.5: HPS national data – derived sample by sex and age-group**

## 4.4 The 2001 Census

The Census of Population in the UK is an important resource for the social sciences, providing a cross-section of data on demographic and socioeconomic circumstances for the majority of the population. It is most notably useful for quantitative geographers, as it is the small-scale geographical units at which the Census is disseminated that provides the most detailed classification of results of any variable (Coombes 1995). Censuses in the UK date back to 1801 and have been held every year since, except for 1941 during World War II (Boyle and Dorling 2004).

The 2001 Census was the most sophisticated yet, providing coverage of populations for especially created small-scale geographic units, 'Output Areas'. Output Areas (UK n=175,434) are built from socially homogeneous clusters of adjacent unit postcodes (based upon household tenure and dwelling type) containing a minimum of 20 resident households and 50 resident persons (Martin 2002). Information on this scale is not available from any other source, and is more reliable than in previous UK Censuses due to the use of statistical imputation method to estimate the characteristics of households and individuals that did not complete the survey (Brown, Diamond, Chambers, Buckner, and Teague 1999). Previous Censuses had not included such techniques and it was left to researchers to address and correct the problem themselves, such as the case of the 'missing million' by Mitchell and colleagues (Mitchell, Dorling, Martin, and Simpson 2002). This development was good news for quantitative medical/health geographers

in the UK, for whom the Census is an important resource that is often looked to for providing the denominator data used to calculate rates of birth, death and disease (e.g. (Exeter, Feng, Flowerdew, and Boyle 2005; Mitchell and Popham 2008)). The 2001 Census of Population will be utilised as denominator data where appropriate in analyses within this thesis.

A second important use of the Census is, in part, derived from one of its perceived shortcomings. Unlike the US Census, it has been traditional in the UK Census not to enquire as to incomes of individuals and households (Martin 2000). There are good reasons for this omission, such as the potentially unreliable answers likely to be given for high earners and the difficulties of whether gross income or net income is more significant (Dorling 1999). Still, as suggested in a previous chapter, the link between socioeconomic position (of which income is one measure) and health is viewed as an established 'fact' commonly referred to as the socioeconomic gradient (Acheson 1998; Black, Morris, Smith, and Townsend 1988; Marmot 2001; Wilkinson and Marmot 2003). Moreover, a large area of research has been dedicated towards associations specifically between income, or lack thereof, and health in both materialistic and psychosocial terms (for just a few recent and notable examples, see: (Benzeval and Judge 2001; Dorling and Barford 2009; Ecob and Davey Smith 1999; Jen, Jones, and Johnston 2009a; Jen, Jones, and Johnston 2009b; Johnston, Jen, and Jones 2009; Lynch, Smith, Kaplan, and House 2000; Marmot and Wilkinson 2001)). As a surrogate for income, medical/health geographers (and researchers in other fields) have often used

ecologically-based measures of socioeconomic deprivation to identify relative affluence amongst individuals and households by the area in which they live (Boyle, Norman, and Rees 2004; Davey Smith, Whitley, Dorling, and Gunnell 2001; Dibben, Sigala, and Macfarlane 2006; Macintyre 2007; Macintyre, Macdonald, and Ellaway 2008a; Norman, Boyle, and Rees 2005). In order to account for some of the important associations between income (as one measure of socioeconomic position) and health, a similar approach is taken by this thesis which is outlined in the next section.

## **4.5 Quantifying socioeconomic deprivation**

Various ecological measures of socioeconomic deprivation have been constructed since the 1980s (Carstairs and Morris 1989a; Jarman 1983; Noble, Wright, Smith, and Dibben 2006; Townsend 1987). As time progresses, so the breadth and detail of the data that has gone into calculating deprivation scores has increased. Townsend, for example, calculated an index based on only four variables from the 1981 Census: i) households without a car; ii) overcrowded households; iii) households not owner-occupied; iv) persons unemployed. In contrast, Noble and colleagues Index of Multiple Deprivation (of which there is a Scotland-based variant called the Scottish Index of Multiple Deprivation (Scottish Executive 2006a)) consisted of six major domains reflecting aspects of deprivation including: i) income; ii) employment; iii) housing; iv) health; v)



education, skills and training; and vi) geographical access to services. Each domain was created from administrative data combined at an area-based level, and each domain is combined to give the overall deprivation index. Advantageously, the IMD and its variants do not depend upon the decennial Census and so can be updated more frequently (Morgan and Baker 2006).

Being ecological, these measures have the advantage in that they can be applied to all individuals and households known to live in those areas for which these indices are calculated. However, as Macintyre notes, these measures do not strictly identify features of the local area, but the characteristics of the local population composition (Macintyre, Maciver, and Sooman 1993). Furthermore, areas identified at the extremes of any particular index may be quite homogeneous, but those areas located towards the middle of the range may contain a more diverse social mix of richer and poorer individuals and households (Macintyre 1997; McLoone 2004; McLoone and Boddy 1994). Such heterogeneity has been argued to be particularly an issue in rural areas, where due to the often sparse geographical distribution of communities, the spatial units need to be rather large to ensure a minimum population threshold. As such, it is very possible that small 'pockets' of socioeconomic deprivation in more remote, rural areas will be masked or hidden (Haynes and Gale 2000). Furthermore, particularly in the context of this thesis dealing with geographic accessibility, the ownership of a car may be more of a necessity rather than a true indicator of income amongst individuals in more remote areas (Martin, Brigham, Roderick, Barnett, and Diamond 2000).

The choice of measure of socioeconomic deprivation for this thesis was the index created by Vera Carstairs and Russell Morris (Carstairs and Morris 1989a; Carstairs and Morris 1989b; Morris and Carstairs 1991), widely referred to as the ‘Carstairs index.’ Although the sophistication of the SIMD would have been preferable, it was not constructed specifically at the small-scale Output Area level at which this thesis is based. The Carstairs index is an alternative measure commonly used in Scotland (Boyle, Exeter, Feng, and Flowerdew 2005; Cox et al. 2007; Cox, Boyle, Davey, and Morris 2007; Levin and Leyland 2006a; Levin and Leyland 2006b; Pearce, Boyle, and Flowerdew 2003).

<i><b>Variable</b></i>	<i><b>Definition</b></i>
<b>Unemployment</b>	Unemployed males 16 and over as a proportion of all economically active males aged 16 and over.
<b>Overcrowding</b>	Persons in households with one or more persons per room as a proportion of all residents in households.
<b>Car Ownership</b>	Residents in households with no car as a proportion of all residents in households.
<b>Low Social Class</b>	Residents in households with an economically active head of household in Social Class IV or V approximated from NS-SEC as a proportion of all residents in households.

**Table 9.6: The 2001 Census-derived variables used to calculate the Carstairs index**

The calculation of the Carstairs index shares similarities with the Townsend index. Four standardised variables taken from the Census: i) households without a car; ii) overcrowded households; iii) persons unemployed; and iv) persons occupying low

occupationally-derived social class positions, the latter of which substitutes households not owner-occupied in the Townsend index. Carstairs and Morris (1991) argued that the use of low social class would better reflect income, potential earnings and job opportunities. Further details on the variables used are shown in Table 9.6. The geographical distribution of the Carstairs index calculated at 2001 Output Area level is illustrated in Figure 9.4, of which it is plain to see that the most deprived areas tend to lie in the more urbanised areas, especially the city of Dundee.

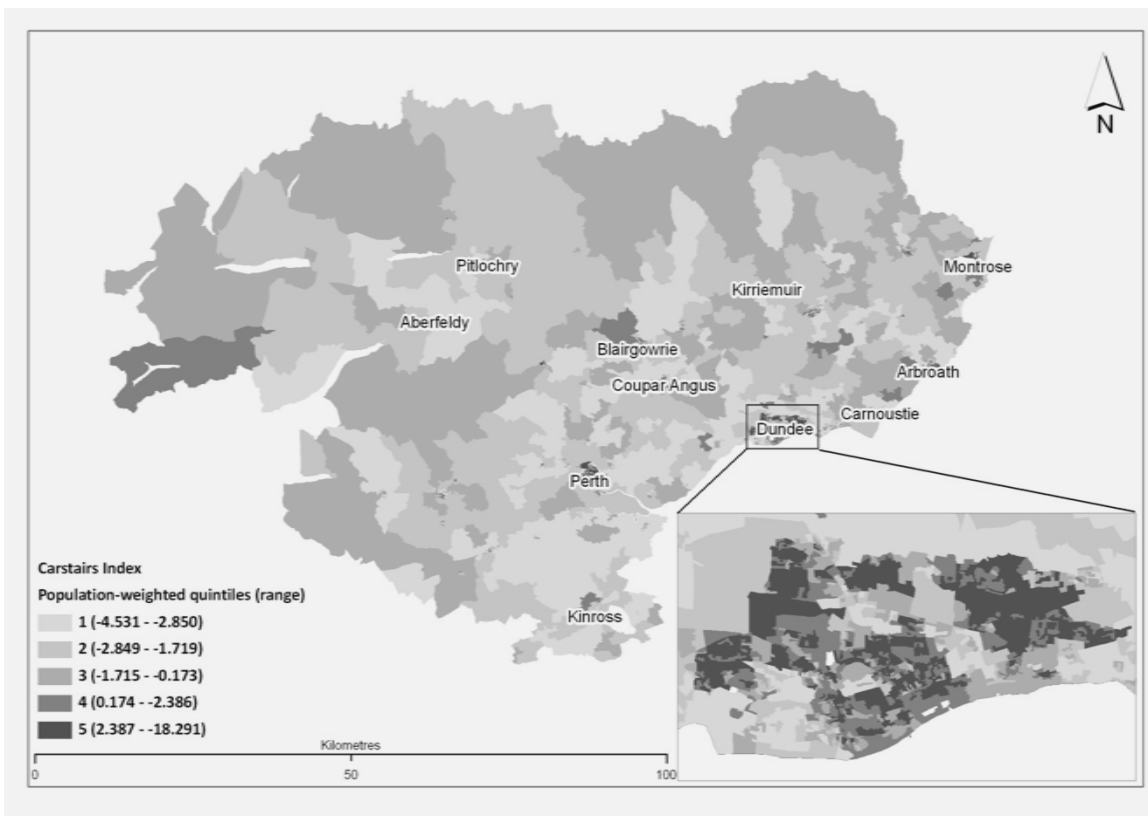


Figure 9.4: The Carstairs index for Output Areas in NHS Tayside (calculated with the 2001 Census)

## **4.6 Quantifying geographic accessibility**

### **4.6.1 Introduction**

So far, the study scene has been set; the data identifying outcomes of patients positively diagnosed with HCV, and the measure of socioeconomic deprivation have each been defined. In this section, attention is turned towards the quantification of geographic accessibility as the main explanatory test variable for the thesis. According to Meade and Earickson (p.473), "geographical methodology has been revolutionised by the information available and the speed and complexity with which it can be manipulated in GIS" (Meade and Earickson 2005). Researchers have been concerned with accessibility before GIS was widely available 'off the shelf' as a methodological tool, with Joseph and Phillips (1984) presenting an extensive review of access to healthcare facilities.

However, such has been the rise to prominence of GIS in facilitating measures of geographic access in the past decade, allowing researchers to query, manipulate and analyse vast quantities of spatial data (Longley, Goodchild, Maguire, and Rhind 2005), many researchers now appear to be persuaded that greater accuracy is achieved with GIS-based measures (Fortney, Rost, and Warren 2000; Haynes, Jones, Sauerzapf, and Zhao 2006; Higgs 2004). Certainly, the diffusion of GIS software and skills has probably accelerated the number of studies exploring spatial patterns of disease and the supply of health services (Gatrell and Senior 1999; Higgs and Gould 2001). It is those GIS-based

measures of geographic accessibility that are examined in this section for which to derive the most appropriate indicator for this thesis.

#### **4.6.2 Measures of geographic accessibility**

Will Gesler, before becoming better known for work on therapeutic landscapes, devised a thesis in the mid-1980s that outlined many of the spatial analyses dominant in the 'medical geography' of that era (Gesler 1986). Since then, GIS has in some ways allowed the enhancement, but for others perhaps aided the trivialisation of quantifying measures of geographic accessibility. The generally easy to develop measures of provider-to-population ratios are a good example to begin with (Joseph and Phillips 1984; Knapp and Hardwick 2000; Susi and Mascarenhas 2002). These ratios are references, usually, to the number of supply locations as the numerator (e.g. GP practices, hospitals, specialist centres) divided by the demand side (e.g. number of individuals or households), all within a given geographical catchment (e.g. healthboards, council areas, local authorities, wards, Output Areas) (Talen and Anselin 1998).

Ratios are very popular not only because of their ease of calculation (they do not really even require GIS in many cases), but also for their intuitive nature when it comes to reporting results. For instance, it is possible to identify areas where the GP to population ratio is less than a recommended level (Connor, Hillson, and Krawelski 1995;

Schonfeld, Heston, and Falk 1972). One example of this method in practice is by Gulliford, who explored association between the number of doctors within health authorities and rates of hospital admissions and infant mortality (Gulliford 2002). Thus, as utilisation is not specified, provider-population ratios are measures of potential geographic accessibility, or, probably more accurately a form of availability (Khan 1992).

However, this so-called intuition is deceptive in the context of geographic accessibility. In the absence of any strict definition of demand, provider-population ratios tend to use the entire population as the denominator, as a measure of potential need rather than actual need. How large the geographic catchment is will also influence the derived ratio (Makuc, Haglund, Ingram, Kleinman, and Feldman 1991). It is assumed that all individuals within any given area have equal access to all supply locations, but in reality this will not be true, especially if larger areas are used.

Given the discussion at length in the previous chapter that other characteristics influence geographic access (e.g. income), that a distance or travel-time decay association could occur (Christaller 1966; Nemet and Bailey 2000), and that individuals may be registered with particular service locations that are not necessarily the closest to their home (Haynes, Lovett, and Sunnenberg 2003), provider-population ratios tend not to control for any of these caveats. It is evident that these limitations will also occur even for small areas. Furthermore, geographic units are imposed from above (the local council, or the researcher), but probably mean little to the individual. People are not

constrained by these normative artificial boundaries and will often utilise supply locations in an adjacent ward or Output Area (Connor, Kralewski, and Hillson 1994).

Moreover, these boundaries are mostly not ad-hoc, but were often originally developed to approach other issues. The common use of electoral wards in UK-based geographical research is a classic example, though similar inferences can be made to the common use of 'postal' geographies. Electoral wards have mean population sizes of around 5,000 residents, but vary considerably from as few as 100 to as many as 20,000 individuals. The boundaries are often odd shapes and unlikely to represent individuals perceptions of the place in which they live. The boundaries are also subject to change, which makes comparisons over time problematic and reliant upon estimation (Flowerdew, Feng, and Manley 2007; Flowerdew and Green 1992; Flowerdew and Green 1994). The limitations of provider-population ratios are thus inherently troubled by the phenomena widely known in geography as the Modifiable Areal Unit Problem (MAUP) (Fotheringham and Wong 1991; Openshaw and Taylor 1981).

The limitations of provider-population ratios had led researchers to explore possible enhancements and alternatives. One example is the floating catchment area, which uses GIS software to create ad-hoc geographic catchments based upon an assumed radii of significance (Luo 2004; Luo and Wang 2003). Whilst this method does to an extent overcome the problem of administrative units, demand is often still assumed to be a centroid (Hewko, Smoyer-Tomic, and Hodgson 2002) of the original units (which for

large geographic scales will be erroneous). Moreover, the radius is often arbitrarily defined and unlikely to reflect variation in propensities for spatial mobility sensu the provider-population ratios (Higgs 2004).

Another example is the gravity model, which was originally developed to predict retail travel and aid urban planners (Hansen 1959; Reilly 1931). Gravity models attempt to model spatial interaction between demand and supply, assuming the supply facilities located closer to demand to have greater significance. Thus, unlike the provider-population ratios and floating catchment areas, gravity models attempt to address the distance-decay issue. Population-weighting can also be applied (e.g. by a measure of deprivation) to amplify areas thought to have greater need for certain supply facilities (Joseph and Bantock 1982).

However, the gravity model is also severely limited. The output is often not as easy to report as provider-population ratios. The complexity of calculation can also be discouraging to researchers, with more sophisticated techniques in GIS software usually necessitated over and above the standard tools available in off-the-shelf packages. Moreover, like the floating catchment area method, gravity models tend to be dependent upon administrative units for centroids and the extent of the radii at which calculations are made is often of arbitrary nature, likely to simultaneously under- and over-estimate the extent of availability. Although there have been so-called “important enhancements” (Guagliardo 2004), by combining gravity models with the floating



catchment area method to produce the “two-step floating catchment area” approach (Radke and Mu 2000; Wang and Luo 2005; Wang, McLafferty, Escamilla, and Luo 2008), the assumptions of radii invoking normatively reasonable distances and travel-times (e.g. (Lee 1991)) are persistent flaws. In short, the benefits of such labour-intensive highly detailed techniques may not (yet) mark a significant improvement upon what less computationally demanding approaches of old can infer.

Each of the aforementioned approaches to measuring geographic accessibility are all potential measures and do not have anything to say with regards to utilisation. In fact, they all have tendencies to measure the availability of supply, or ‘spatial accessibility’ in the sense used by Guagliardo (Guagliardo 2004), rather than geographic access to, for instance, the nearest possible supply location. Furthermore, only the more recent method do much to tease out substantial variation in geographic access caused by topography, such as large lakes or mountainous terrain that would have significant ramifications for travel. The more recent do this by taking into account travel impedance.

Measures of travel impedance might be viewed as more direct measures of geographic accessibility. These involve the use of a demand location, such as the centroid of an Output Area, and the calculation of the displacement between that centroid and the nearest supply facility (e.g. GP practice or hospital). Such displacement may be measured by straight-line distance (the so-called ‘crowfly’ distance) (e.g. (Boyle, Kudlac,

and Williams 1996b; Jordan, Roderick, Martin, and Barnett 2004)) or, as is far more popular now, by distances and travel-times along a specified road network (e.g. (Bamford, Dunne, Taylor, Symon, Hugo, and Wilkinson 1999; Brabyn and Gower 2002; Brabyn and Skelly 2002; Charlton, Fotheringham, and Brunsdon 2001; Fortney et al. 1995; Fortney, Rost, and Warren 2000; Fortney, Rost, Zhang, and Warren 1999; Haynes, Pearce, and Barnett 2008; Lovett, Haynes, Sunnenberg, and Gale 2002; Macintyre, Macdonald, and Ellaway 2008a; Macintyre, Macdonald, and Ellaway 2008b; Martin, Wrigley, Barnett, and Roderick 2002; Parker and Campbell 1998; Perry and Gesler 2000; Rosero-Bixby 2004; Slack, Cumming, Mar, and Timmins 2002)).

In the UK, Lovett and colleagues have demonstrated the level of skill and the many datasets to be drawn upon for developing such indicators of road network displacement, which, on the face of it, appear deceptively simple. The general approach for calculating one popular measure, of travel-time to the nearest GP, was shown to require data on demand and supply locations which are then allocated to a road network (e.g. the 1:200,000 Bartholomew Road Atlas road network). Each type of road in the network (from motorways to minor roads) are awarded average speeds depending upon whether they are predominantly urban or rural, from which the time taken to traverse the quickest possible route from A to B can be calculated with programming in a GIS (Lovett, Haynes, Sunnenberg, and Gale 2002). The result is that each demand location has an estimated minimum travel-time to the nearest supply facility, which can then be mapped and analysed (Figure 9.5).

Thus, employing a road network implicitly goes some way to solving the problem of topography in that it takes into account topography and road infrastructure (i.e. access to fast motorways or dependency upon slow b-roads) that could exacerbate geographic inaccessibility in real life (Lin, Allan, and Penning 2002). A common concern of this approach is the assumption that all individuals have access to private transport, but Lovett and colleagues (and also Martin and colleagues (Martin, Wrigley, Barnett, and Roderick 2002)) describe ways to incorporate public transport data if it is available.

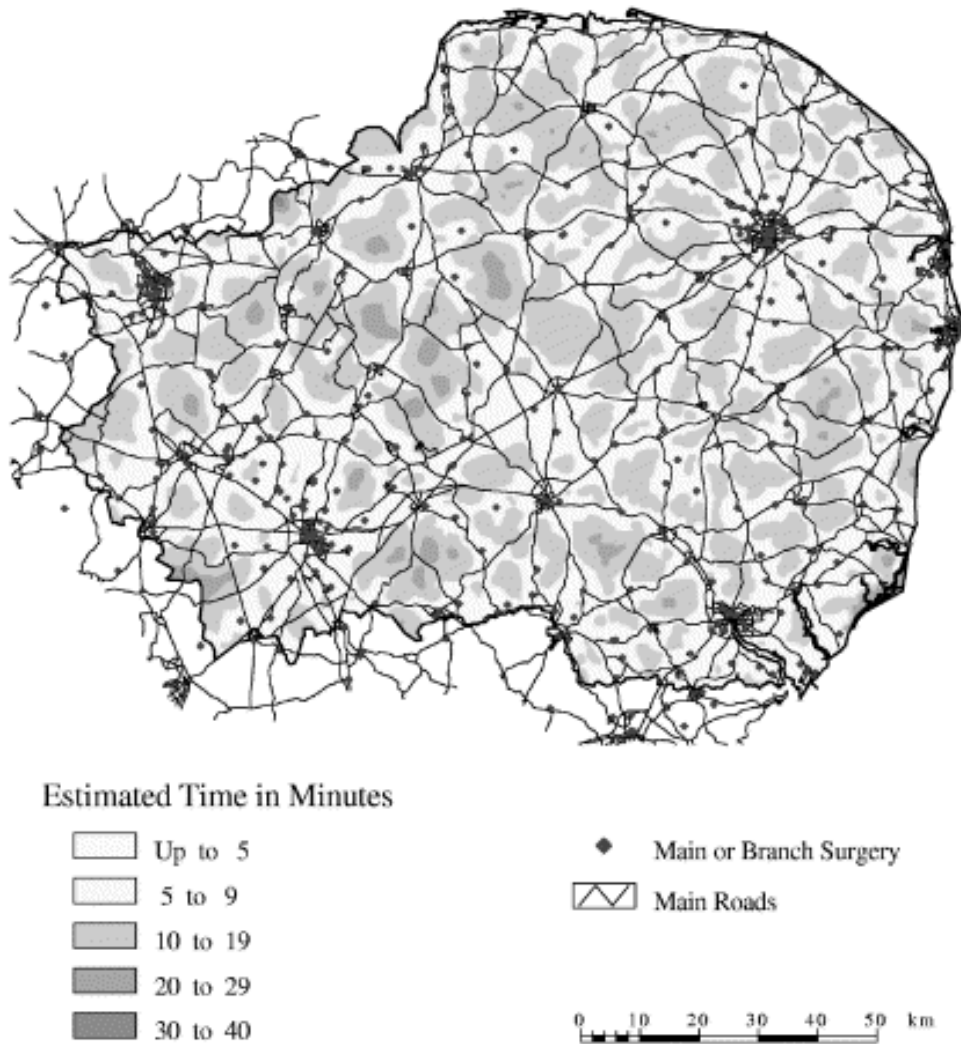


Figure 9.5: Travel-time to the nearest GP practice in East Anglia (Source: (Lovett, Haynes, Sunnenberg, and Gale 2002))

However, as the authors suggest, availability of the public transport data is only the first problem. Integration of this data into GIS accessibility models is not trivial. For instance, assumptions need to be made about connectivity between services. If an individual is to change buses halfway through the journey, and the connection requires walking half a mile from one station to another, walking speed must also be taken into account. In the context of visiting a GP when an individual is feeling unwell, assumed walking speeds are even more unrealistic than normal and it is also a significant possibility that alternative, more accommodating arrangements may be sought (e.g. a taxi, or a friend's car). Travel-impedance measures incorporating public transport are still very much in the early stages of development.

Furthermore, in favour of using travel-impedance measures as an alternative to the previously discussed ratio-based indicators, it may be reasonable to assume that choices of GP for communities in more remote, rural areas will be limited to the one located closest. Indeed, a previous study has shown that individuals in more rural areas were more likely to be registered with their closest GP practice compared with those in urban areas (Haynes, Lovett, and Sunnenberg 2003). In urban areas, where travel-times or distances are short, the greater availability of potential supply facilities if an individual is willing to travel a little further is probably a reason for the more detached, consumerist approach to healthcare-seeking behaviour (Farmer et al. 2006; Higgs 1999).

In the review of evidence on health outcomes influenced by geographic accessibility in the previous chapter, almost all studies utilised a measure of travel-impedance. A significant advantage of this method to the ratio-based approaches is that the same techniques can be applied to measuring potential geographic access as well as utilisation. The only major difference is that whilst potential is usually the nearest possible supply facility, utilisation is the travel-impedance to a known destination. That there are more studies of potential rather than service utilisation (McLafferty 2003) is, therefore, not due to a lack of technique available to construct and analyse geographic access measures, but a porosity of sufficiently detailed data. Travel-time has been identified as the measure of travel-impedance most likely to reflect that actual journeys people will take (over and above straight-line and network distances) (Haynes, Jones, Sauerzapf, and Zhao 2006), though some caution should be held as these estimates do not always marry well with self-reported travel-times (Macintyre, Macdonald, and Ellaway 2008b).

It is with all of these merits and drawbacks in mind that for this thesis, the most appropriate measure of geographic accessibility to utilise is travel-time-impedance, for its flexibility between potential and utilisation studies, intuitive interpretation, and potential for comparison and replication in other studies with relative ease. The steps in its construction are discussed now.

### **4.6.3 Development of a measure of geographic accessibility**

In order to estimate travel-time, supply and demand needed to be defined. Supply was the postcode unit of every GP practice in NHS Tayside and those within a 10km buffer around (to account for edge effects). A complete list of GP practices was available from Information Services Division (ISD) Scotland through personal communication, correct up to December 2006. Unfortunately, previous registers are updated but not archived, so the extent to which geographic access to the nearest GP practice may have varied over time was not possible. No distinction was made between practices (e.g. presence of female GP) as this data was also unfortunately not available. The postcode unit of the Ninewells Hospital and Medical School was used to identify the HCV specialist unit. The approach to defining demand involved calculating the geometric centroid of each Output Area falling within NHS Tayside (n=3380), to which the travel-time estimates could be joined to the other patient records and 2001 Census. Output Area shapefiles were extracted from the UK Borders website (<http://www.edina.ac.uk/ukborders/>). Figure 9.6 illustrates the spatial extent of supply and demand locations within NHS Tayside, of which the clustering of centroids in the 'urban' areas and Dundee especially is reassuring.

The second major step was to prepare a suitable road network. With permission from the Ordnance Survey, the Integrated Transport Network (ITN) (Ordnance Survey 2008) with coverage for the whole of Scotland was made especially available. The ITN is the

most detailed, accurate and up-to-date digital road network available for the whole of Great Britain. Average road speeds were allocated to different types of road (e.g. motorway, a-road, b-road, etc) and whether the different segments of roads were in predominantly urban or rural areas. ArcGIS (v8) software was used to extract road types and classify as urban or rural using the Scottish Executive Urban/Rural 6-Fold Classification (Scottish Executive 2006b) for Datazones (Flowerdew, Feng, and Manley 2007). Average road speeds used in the construction of the aforementioned resource were also utilised (see Table 9.7). The geographical extent of the major road network is also illustrated in Figure 9.6, of which it is evident that access to major transit routes becomes rarer in the more remote, rural areas to the north and west. For consistency with ArcGIS software, these road speeds were converted into km/minute (as estimated travel-time outputs would also be in minutes). Road lengths were calculated in km.

ROAD TYPE	RURAL [m/hr]	URBAN [m/hr]
Motorway	65	44
A road	40	19
B road	34	16
Minor and other road	25	14
Non-network road	25	14
Pedestrian road	25	14
Private road - acc. to public	25	14
Private road	25	14
Ferry	22	22

Table 9.7: Average road speeds, by road type and urban/rural classification (Source: (Scottish Executive 2006b))

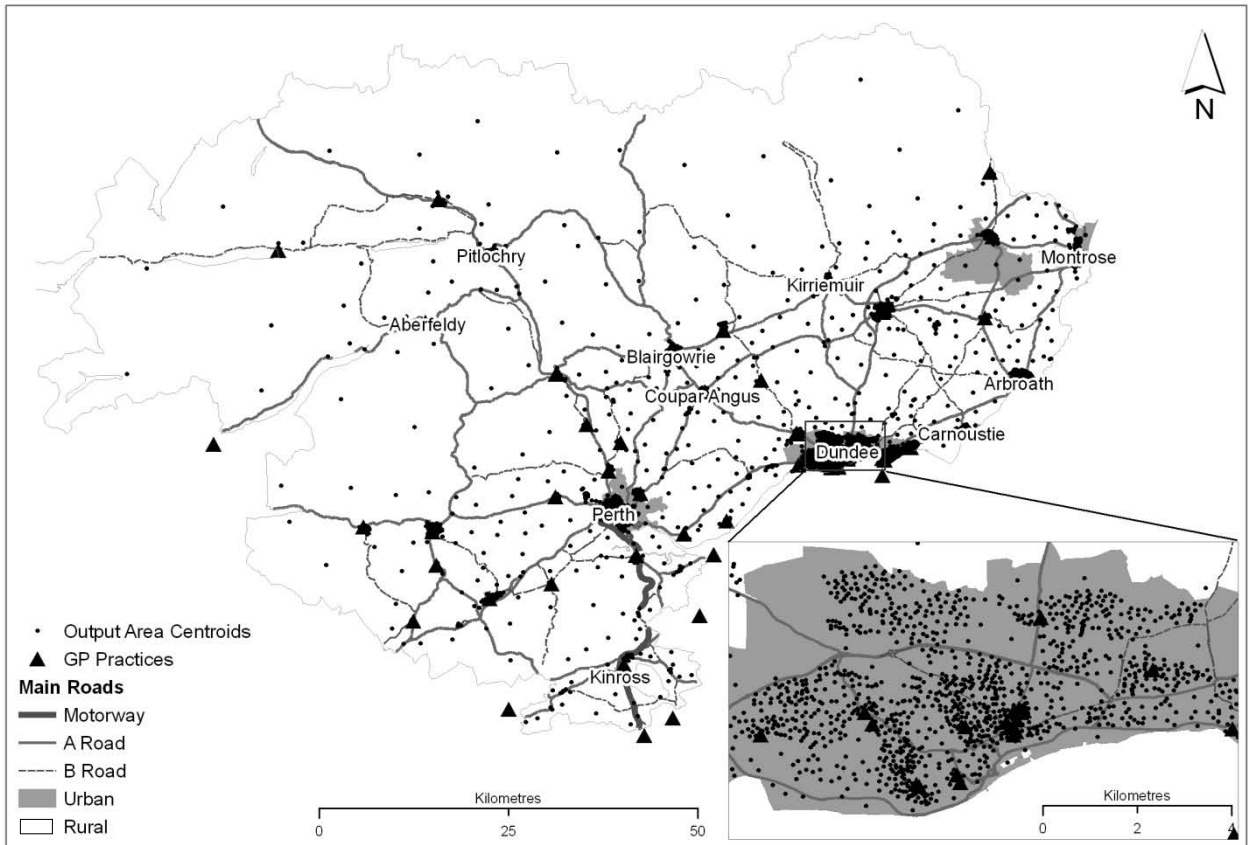


Figure 9.6: Locations of GP practices, Output Area centroids, and main roads by type and urban/rural category in NHS Tayside

ArcINFO GIS command-line software was used to convert the now classified road network (arcs), supply and demand locations into coverages. Each supply and demand location needed to be assigned to the nearest node on the road network (typically, junctions) using the ArcINFO software. To ensure that the displacement between locations and nodes was not excessive, the road network was fragmented into smaller arcs, creating a regular set of nodes. Thus, the maximum length of any arc was limited to 12km and the maximum displacement of any location and node at 3.5km (the vast majority of locations were less than 100m from the nearest node). These values correspond favourably with (Lovett, Haynes, Sunnenberg, and Gale 2002), where the maximum displacement was never more than 5km. Reducing the maximum arc length



could have substantially increased the overall number of arcs and significantly increased the computer resources required to process the data, so this degree of proximity was considered at a sufficient level to prevent biases in the estimation of travel-times.

Once all supply and demand points had been assigned to nodes on the road network and the relative displacement calculated (km), travel-times of these displacements were estimated using the average “Minor and other road” speeds. Then, user-defined Arc Macro Language (AML) scripts were used to find the shortest travel-time between each demand and supply nodes. Therefore, for each Output Area centroid, the travel-time between the centroid and assigned road network node, the travel-time from a GP practice postcode unit and the assigned road network node, and the travel-time between each of the aforementioned nodes were added together to give the most accurate overall travel-time estimate. Figures 9.7 and 9.8 illustrate the population-weighted (Census-based) quintiles for travel-time estimates to the nearest GP practice and to Ninewells Hospital and the HCV specialist centre for NHS Tayside respectively.

As discussed earlier (p.186), an important limitation of this measure of geographic access along with most others is that they only relate to private transport. In addition to the theoretical reasons given, the omission of public transport information in this measure was also due to the lack of information available at the time of their production. The ‘Traveline Scotland’ ([www.travelinescotland.com](http://www.travelinescotland.com)) service that now offers information on public transport times was only in developmental stages at the time of analyses presented here.

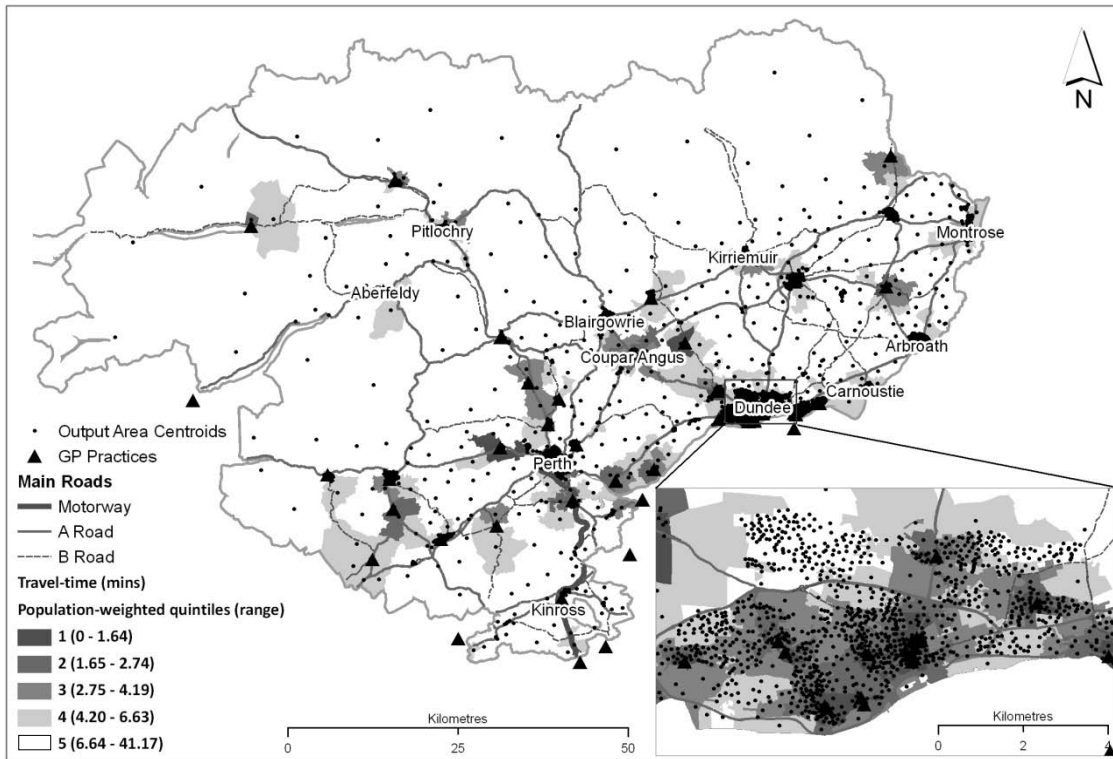


Figure 9.7: Estimation of travel-time to the nearest GP practice in NHS Tayside

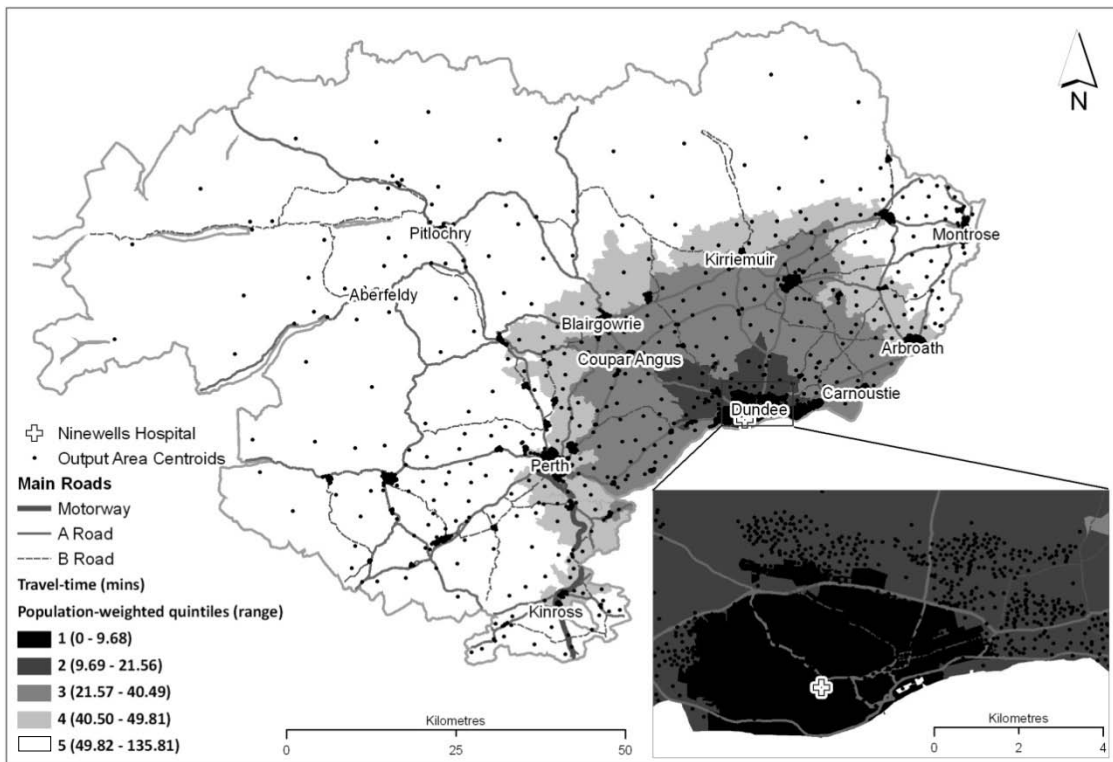


Figure 9.8: Estimation of travel-time to the HCV specialist centre in NHS Tayside

# **5. Does geographic access to healthcare influence the detection of HCV?**

## **5.1 Introduction**

In previous chapters, the situation with regards to the low rates of detection of HCV in Scotland has been described. Several studies have explored similar situations in other countries, notably Australia, identifying various social factors such as sex, age and history of intravenous drug use (IDU) that are thought to be associated with the chances of being diagnosed (Hopwood and Southgate 2003). These factors are probably also involved in the shortfall in Scotland. I have put forward a case which suggests that geographic access to primary healthcare, largely ignored in the context of HCV detection so far, may be a significant contributing factor. More specifically, individuals with further to travel to their nearest GP may be more likely to delay seeking consultation or not get diagnosed at all, in contrast to those with more favourable geographic access. Only two studies (Monnet et al. 2006; Monnet et al. 2008) have investigated this

hypothesis so far, each located within a region of France, both suggesting supportive evidence though not without significant limitations, particularly with regards to controlling for socioeconomic position and the prevalence of IDU risk factors. I have argued that the association between geographic access to primary healthcare and rates of HCV detection in these studies may be artifactual in the absence of the aforementioned controls.

In Scotland, where topography and infrastructure exacerbate the remoteness of rural communities, HCV detection rates may be lower amongst individuals lacking geographic access to primary healthcare. This chapter details the analytical steps made in application of this hypothesis to the population of NHS Tayside. In contrast to the France-based studies, the analysis here utilises a widely-recognised measure of socioeconomic deprivation, the Carstairs index (Carstairs and Morris 1989a), the construction of which has already been itemised in the method chapter.

The second noteworthy innovation over the France-based studies is the use of patient records of opiate substitution therapy (OST) to identify individuals that are known to the medical profession to have a history of IDU. OST, which refers to prescriptions for methadone and buprenorphine, is used in the rehabilitation of people with a history of IDU and can be prescribed and dispensed by GPs, private doctors and specialist centres in the UK (Solberg, Burkhart, and Nilson 2002). The significance of augmenting the models for OST is in the exploration of whether any possible association between

detection and geographic access to primary healthcare is consistent across groups, or disproportionately affects one group more than another, or maybe influences neither. Such a distinction helps to identify possible selection effects, as we would expect a greater number of individuals with a history of OST to be located in more built-up urban areas where travel-times to primary healthcare are short, reflecting the greater prevalence of IDU risk factors, incidence of HCV and the IDU-targeted screening programmes.

If geographic access to primary healthcare is associated with HCV detection in both the OST and non-OST groups, this could be highlighting support towards poor geographic access as a factor limiting detection. If, however, geographic access to primary healthcare is only significant for those individuals with a history of OST, this result would be less convincing, maybe simply a reflection of higher HCV prevalence in urban areas, sensu the critique of Monnet and colleagues studies.

Hence, the analyses in this chapter are aimed towards gathering answers to two key questions:

1. To what extent is poor geographic access to primary healthcare associated with lower rates of HCV detection?

2. To what degree is any influence of geographic access on detection experienced by individuals with and without a history of OST?

## 5.2 Methodological approach

An ideal study design to answer these questions would involve an investigation of individuals that have been positively diagnosed with HCV, relative to the number of antibody-negative test results, or the overall number of tests for HCV. Unfortunately, the data is limited to only positive HCV diagnoses and so, an alternative approach is required.

The incidence of HCV is relatively rare in comparison to other health conditions, such as CHD or stroke. Detection of HCV is rarer still. We already have a good idea that age and sex are important social factors to consider when measuring rates of detection and one statistical approach, the 'direct' method, would be to calculate age-sex standardised ratios for small geographical areas. More specifically, this is the number of detected individuals per 100,000 residents, calculated by multiplying the age-sex-specific detection rate for one geographical area by the proportion of that particular age-sex-specific group in the 'standard' population. These results are then summed for all age-sex-specific groups. However, this direct approach is unsatisfactory in the case, as it is

dependent upon a fairly large number of detected individuals within the observed sample (Bland 1988), which is not the case for individuals detected with HCV (n=890 in our data) in Tayside (N=~400,000+).

Another commonly used approach, the standardised morbidity ratio (SMR) (Boyle, Norman, and Rees 2004; Exeter, Boyle, Feng, and Boyle 2009; Exeter, Feng, Flowerdew, and Boyle 2005; Norman, Boyle, and Rees 2005), is known as 'indirect' and more suitable when the observed number of detected individuals is fairly small. An SMR is a ratio (formula given below) of the number of detected individuals (the observed) by the number of expected to be detected for each age-sex-specific group, multiplied by 100 (Bland 1995). '100' represents the average rate for the greater area of investigation, with SMRs larger than 100 denoting poorer rates of detection and those less than 100 indicating more favourable rates.

$$SMR = 100 \times \frac{\textit{observed}}{\textit{expected}}$$

The expected denominator figure is calculated by dividing the total number of detected individuals per age-sex-specific group by the comparable total population. The age-sex-specific group population for each geographical area is then multiplied by the corresponding detection rate, giving the expected age-sex-specific group number of

detected individuals. Summing these responses together per geographic area gives the total expected number of detected individuals.

However, there are also problems with the use of SMRs for small areas (for further discussion, see (Julious, Nicholl, and George 2001)). The most important for this study is that such is the rarity of HCV detection, we will probably be dealing with very small observed and expected numbers per geographic area. Such minute numbers render the SMR very sensitive to slight differences. For instance, an area has four individuals expected to be detected with HCV where only two individual were observed giving an SMR of 50, interpreted as half the regional rate. However, were the expected number increase or decrease by just a couple of individuals, such as dropping to one, the SMR would escalate to 200, twice the regional rate and a very different conclusion. In other words, SMRs are highly troubled by the stochastic nature of the data, referred to as the 'small number problem' (Gatrell 2002). For this study, a more robust approach is needed.

A statistical method that is more appropriate for the investigation of rare events such as the detection of HCV is the Poisson regression method (Boyle, Flowerdew, and Williams 1997). It is particularly suitable when the response variable is a count (i.e. the number of detected individuals per geographic area), when there is a large number of geographic areas that have zero counts (i.e. no detected individuals) and when such events occur independently of each other (Lovett and Flowerdew 1989). In a Poisson



regression model, the natural logarithm of the maximum likelihood estimate is equal to the linear combination of the corresponding values of the explanatory variables. When only one explanatory variable is examined, the predicted value of the response variable is the maximum likelihood estimate:

$$\ln(\hat{\lambda}_i) = \beta_0 + \beta_1 x_1$$

This formula can be expressed alternatively in the form of a linear regression model:

$$\hat{\lambda}_i = \exp(\beta_0 + \beta_1 x_1)$$

Relative to the use of SMRs, which were adopted as the preferred index of the Registrar General's decennial supplement in 1951 (General Register Office 1958), the use of Poisson regression in health research has been more recent. An early example of Poisson regression method was by Lovett and colleagues in a study of explanatory factors for ischaemic heart disease (IHD) mortality in England and Wales, finding higher rates among older men, overcrowding among other variables. Comparing the results of the Poisson method with a log-normal approach, Lovett and colleagues demonstrated

superior goodness of fit and more reliable results with the Poisson method (Lovett, Bentham, and Flowerdew 1986).

More recently, in an investigation of the hypothesis that mortality rates were highest in geographic areas experiencing a decline in population (or so-called “shrinking areas” (Davey Smith, Shaw, and Dorling 1998)), Exeter and colleagues used Poisson regression method to show that the negative association between population change and mortality was rendered statistically insignificant after adjusting for socioeconomic deprivation (Exeter, Feng, Flowerdew, and Boyle 2005). Most applicable to the research questions in this chapter, Poisson regression has also been previously used the context of geographic access to healthcare (Jones and Bentham 1997; Jones, Bentham, and Horwell 1999), each demonstrating a greater risk of asthma-related mortality amongst individuals living further from major health service units.

Given the inadequacy of SMRs for dealing with small numbers and the recent evidence in favour for Poisson regression method, this chapter adopts the latter approach to modelling HCV detection rates.

## 5.3 Study specification

### 5.3.1 Study sample and setting

The data for use in the following analyses was discussed in detail in previous chapter, but the specifics for this particular study are now outlined. Anti-body positive HCV patient records (n=890) were extracted from the 'Epidemiology for Liver Disease in Tayside' (ELDIT) database (Steinke et al. 2002a; Steinke et al. 2002b). Each patient was at least 15 years old and had full age, sex, and 2001 Census Output Area (Martin 2002) of residence data. To reiterate, this sample reflects those patients that have been positively diagnosed, or detected, and does not include anti-body negative diagnoses, incidence or prevalence of HCV. Furthermore, patients diagnosed when in prison were omitted from the analysis because geographic access to healthcare would not have been relevant to their screening. Patients within the ELDIT living in Output Areas outside the boundary of NHS Tayside were omitted, as appropriate equivalent patient records from neighbouring healthboards (Fife, Grampian) were unavailable and keeping these selected Output Areas in the model would therefore suffer underestimated counts.

NHS Tayside is a large area of Scotland, encompassing the city of Dundee, Perth and Forfar, with the smaller towns of Pitlochry and Aberfeldy situated further north where communities are more rural and remote. This mixture of densely-populated and

sparsely populated areas makes NHS Tayside a suitable area to test association between geographic access to healthcare and HCV detection rates.

### **5.3.2 Variable definition**

The response variable in Poisson regression method takes the form of count data. Thus, individuals diagnosed with HCV were aggregated into age-sex specific groups per Output Area. The number of Output Areas fully within NHS Tayside numbered 3380 and the age-sex-specific groups were as follows: men/women aged 15-24; 25-29; 30-34; 35-39; 40 + (n=10). The total N was 33800. An equivalent age-sex-Output Area-specific population was extracted from the 2001 Census for use as a denominator (population aged 15+ n = 322,219).

Two other response variables were calculated. A history of OST was identified from prescriptions data held within the ELDIT, from which dispensed drug history for each patient could be gleaned. Separate age-sex-Output Area counts of patients with and without a history of OST were aggregated (OST n = 420; non-OST n= 470).

The main explanatory test variable was geographic access to primary healthcare, the calculation of which has already been discussed. In brief, this measure was the road network travel-time calculated using average speeds by road type, from the geometric

centroid of an Output Area to the nearest GP practice identified by easting and northing coordinates. Therefore, every individual located within a single Output Area were defined to have the same travel-time. Lower travel-times indicate more favourable geographic access to primary healthcare.

In control for modifying influences on geographic accessibility, the Carstairs index of socioeconomic deprivation was used (Carstairs and Morris 1989a) in the absence of individual-level data on employment, income or other measures of socioeconomic position. This ecological measure of deprivation, the calculation of which has already been discussed, also helps to adjust the model for the spatial distribution of risk factors associated with IDU (Craine, Walker, Williamson, Brown, and Hope 2004; Craine, Walker, Carnwath, and Klee 2004; Hutchinson et al. 2004). Higher scores denote greater relative disadvantage and the prevalence of risk factors.

### **5.3.3 Analysis specification**

Three major Poisson regression models were fitted, corresponding to the three response variables: i) all detected patients; ii) OST patients; iii) non-OST patients. In each model, the natural logarithm of the age-sex-Output Area-specific group calculated denominator population was included as an offset. Univariate models were fitted initially to explore general association with each of the explanatory variables. Further

modelling fitted explanatory variables incrementally in build up to fully adjusted models. Models were checked for over-dispersion. For modelling purposes, the travel-time measure was calculated as natural logarithm to reduce problems of skewness. Deprivation and travel-time quintiles (calculated for NHS Tayside and population-weighted) were included to explore for potential non-linear associations.

## 5.4 Descriptives

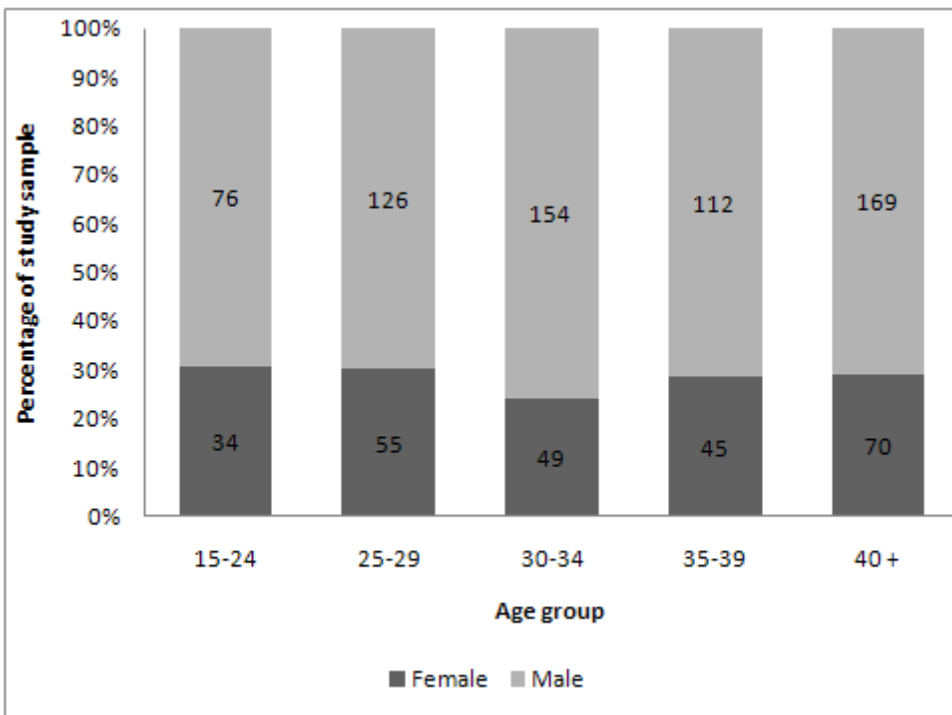
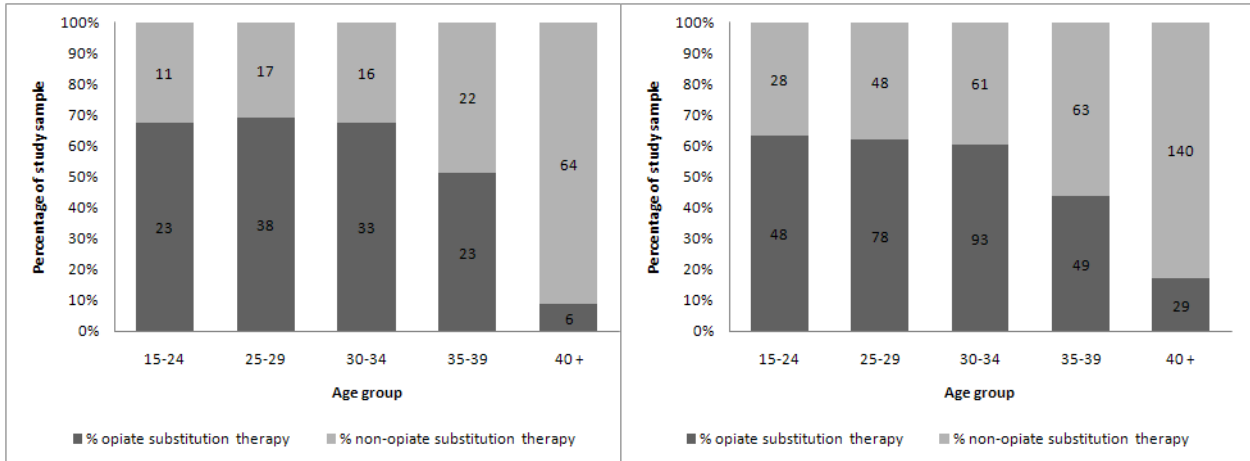


Figure 10.1: People diagnosed with HCV in NHS Tayside (1991-2003), by age group and sex (total number of patients for each sex and age group are illustrated within bars)

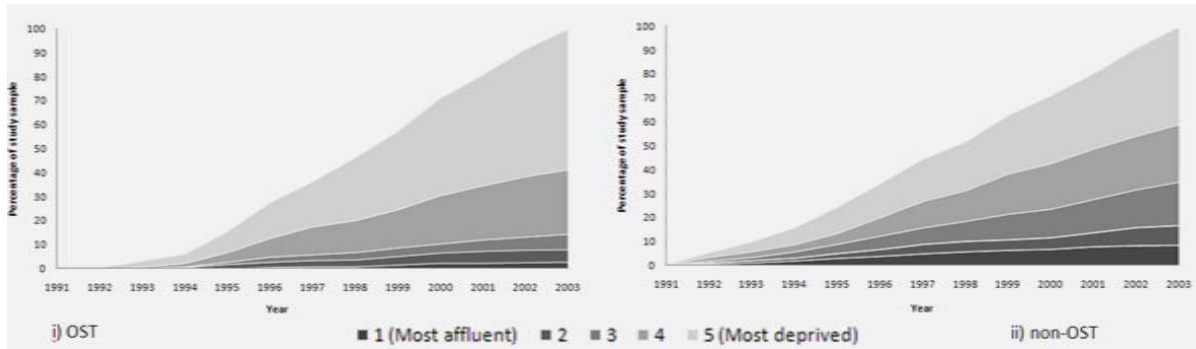


Female

Male

**Figure 10.2: People detected with HCV in NHS Tayside (1991-2003), by age group and opiate substitution therapy (total number of patients for each sex and age group are illustrated within bars): female and male**

Of 890 people detected with HCV, 71.6% were male to 28.4% female. These proportions were relatively consistent for each age group, varying between 69% and 75% (Figure 10.1). Patient records of OST were also reasonably consistent between sexes, with fairly high percentages reported in age groups 15-24; 25-29; and 30-34. OST was notably less common for patients aged 35-39, and substantially less (<20%) for those aged 40 and over (Figure 10.2). These trends are reassuring as they reflect findings from other studies (Craine, Walker, Carnwath, and Klee 2004; Hutchinson et al. 2006), especially since younger persons are more likely to have a history of IDU. The lower OST prevalence observed in older age groups is indicative of greater aetiological variation, which will include many patients that were infected with HCV through blood transfusion and also those infected through IDU that have not received/required OST (e.g. individuals trying IDU once, but never becoming addicted).



**Figure 10.3: Cumulative percentage detection of HCV, by year and Carstairs deprivation quintile (population-weighted) for NHS Tayside: i) patients with a history of opiate substitution therapy; ii) patients without a history of opiate substitution therapy**

Figure 10.3 demonstrates the cumulative detection of HCV over time, in which it is clear that a major proportion of all patients suffered high levels of (Carstairs) socioeconomic deprivation. It is also evident that the patients with a history of OST tended to be geographically segregated into more deprived areas, whereas the non-OST sample which were relatively more evenly distributed by comparison (e.g. 59% OST patients in the most deprived quintile to 41% for non-OST).

We also found that the majority of more deprived Output Areas had reasonably good geographic access to primary healthcare, with a weak negative non-linear correlation ( $R^2=0.035$ ) between travel-time and Carstairs deprivation (Figure 10.4). Residents of OAs with longer travel-times tended to be more affluent (maximum travel-time reported = 41.2 minutes) and situated in more remote, rural areas in the north of NHS Tayside (Figure 10.5). Far greater heterogeneity in the deprivation variable was observed in areas with favourable geographic access to primary healthcare, situated mostly in and around the settlements near the city of Dundee. Accordingly, HCV



prevalence was expected also to be higher in some areas with good access to a GP and lower in areas where access was generally less-favourable.

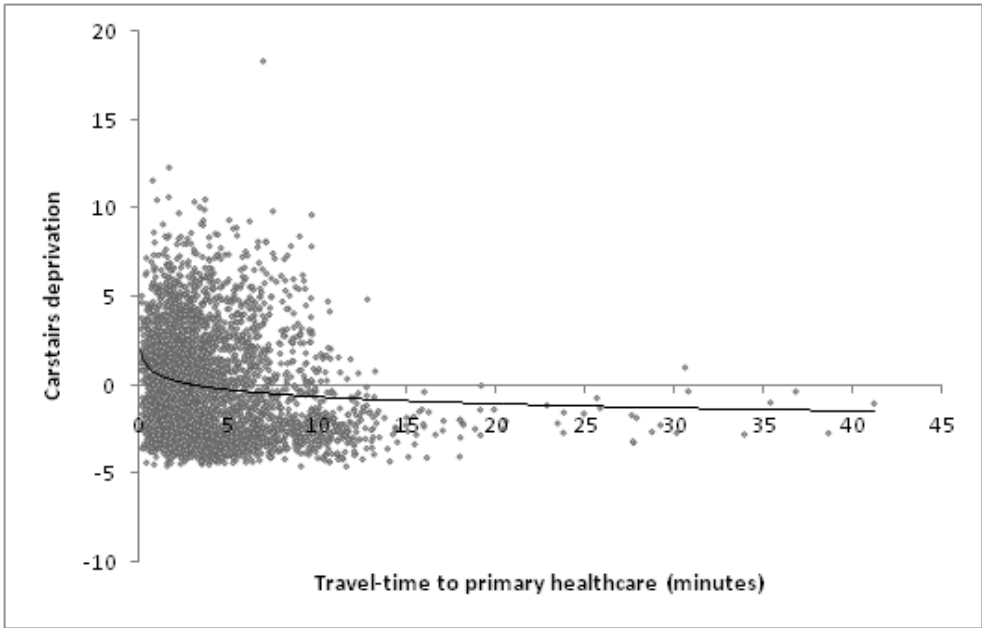


Figure 10.4: The statistical association between Carstairs deprivation and travel-time to the nearest GP ( $R^2 = 0.035$ ), including logarithmic trend line

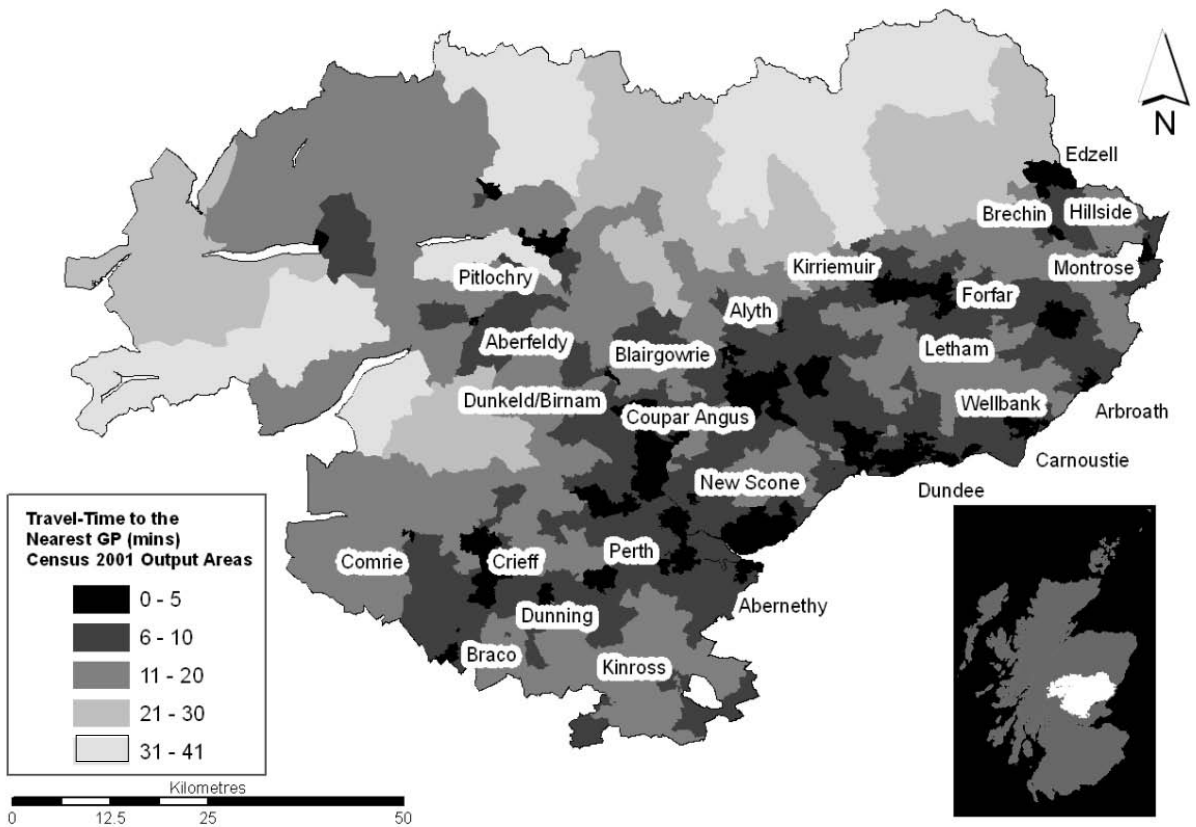


Figure 10.5: Travel-time to the nearest GP in NHS Tayside (location in Scotland illustrated, bottom right)

## 5.5 Univariate associations (full-sample)

### 5.5.1 Introduction

To get an initial idea of associations between response and explanatory variables, univariate Poisson models of HCV detection are fitted with the log Census population as an offset. The notation for the null model is:

$$\begin{aligned} \text{hcvtot}_i &\sim \text{Poisson}(\pi_i) \\ \log(\pi_i) &= \text{logpoptot}_i + \beta_0 \text{cons} \end{aligned}$$

where 'hcvtot' denotes the full-sample of detected patients is being used as the response variable, 'logpoptot' is the offset, and ' $\beta_0$ ' the parameter for the model constant.

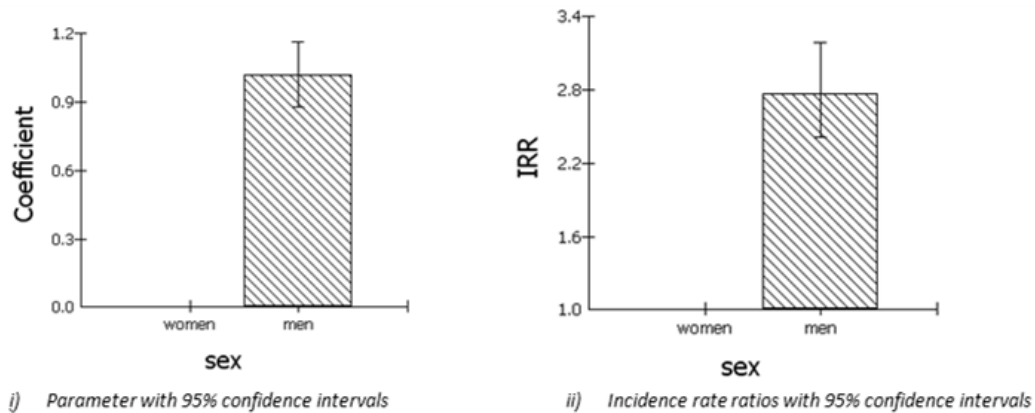
### 5.5.2 Sex

Sex was fitted to the Poisson model as a binary variable, with women (=0) set as the baseline and men (=1) the fitted response.

$$hcvtot_i \sim \text{Poisson}(\pi_i)$$

$$\log(\pi_i) = \log\text{pop}tot_i + -6.603(0.063)\text{cons} + 1.019(0.074)\text{men}$$

The parameters are regression coefficients, whereas the number in brackets denotes the standard error. Positive parameters indicate positive association with HCV detection. Negative parameters indicate the inverse. In this case, the parameter for men is 1.019, and the standard error equalled 0.074. This indicates that the log- E mean count for men was higher than that for the base category of women. In other words, men are more commonly diagnosed with HCV in NHS Tayside than women after adjusting for the underlying population distribution. This association is made clearer graphically in Figure 10.6.



**Figure 10.6: Univariate model i) coefficients and ii) incidence rate ratios: sex (full-sample)**

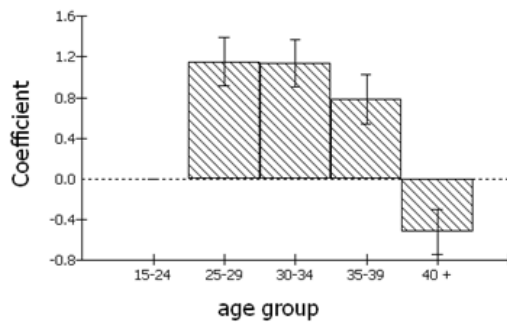
The graphical portrayal of the regression coefficient in Figure 10.6 (i) shows clearly that men are more likely to be detected than women. This association is statistically significant to 0.05 as the lower of the 95% confidence intervals is well above the zero mark. To aid interpretation, the Poisson regression coefficient and confidence intervals can be exponentiated to what is referred to as an incidence rate ratio (IRR). With the

rate of detection for women set to 1, we can say that rates of HCV detection for men are 2.8 times higher (IRR=2.766).

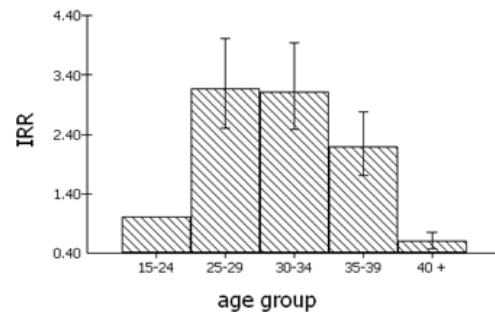
### 5.5.3 Age group

$$hcv_{tot_i} \sim \text{Poisson}(\pi_i)$$

$$\log(\pi_i) = \text{logpop}_{tot_i} + -6.221(0.095)\text{cons} + 1.154(0.121)25-29 + 1.138(0.118)30-34 + 0.781(0.124)35-39 + -0.524(0.115)40 +$$



i) Parameter with 95% confidence intervals



ii) Incidence rate ratios with 95% confidence intervals

**Figure 10.7: Univariate model i) coefficients and ii) incidence rate ratios: age group (full-sample)**

The next variable to analyse was age group, fitted to the Poisson model as a categorical variable, with 15-24 year olds set as the baseline and all other groups as the fitted responses. Positive coefficients were noted for individuals aged 25-29; 30-34; and 35-39, whereas a negative coefficient was observed for the 40+ group. Graphically (Figure 10.7), it is clear that HCV detection rates are significantly greater amongst 25-39 year old age groups relative to 15-24 year olds as the 95% confidence intervals do not overlap baseline. Lower rates of detection for individuals over 40 are also statistically significant. Furthermore, since the 95% confidence intervals for 25-29, 30-34 and 35-39

year olds do overlap, we cannot state with certainty that the rates of detection for any of these three groups are higher or lower in comparison with each other. Since there is no overlap between these groups and the over 40s, however, it is highly probable that the rate of detection for the latter is statistically lower than the former.

#### 5.5.4 Deprivation

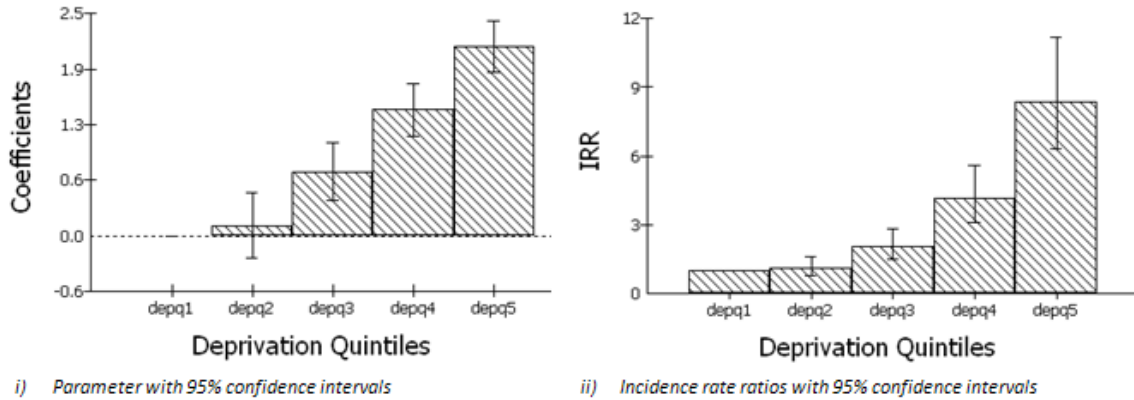
The Carstairs index of socioeconomic deprivation was fitted to the Poisson model in two separate formats (and separate models). First, as a continuous variable, the coefficient was positive (0.229) indicating a one unit increase in the HCV detection rate corresponded to a one unit increase in the deprivation index. The very small standard error meant that this association was statistically significant below the 0.001 level.

$$\begin{aligned} \text{hcvtot}_i &\sim \text{Poisson}(\pi_i) \\ \log(\pi_i) &= \text{logpoptot}_i + -6.214(0.039)\text{cons} + 0.229(0.009)\text{carstairs} \end{aligned}$$

*(continuous)*

$$\begin{aligned} \text{hcvtot}_i &\sim \text{Poisson}(\pi_i) \\ \log(\pi_i) &= \text{logpoptot}_i + -7.191(0.137)\text{cons} + 0.113(0.188)\text{depq2} + 0.720(0.167)\text{depq3}_i + \\ &\quad 1.421(0.153)\text{depq4}_i + 2.129(0.145)\text{depq5}_i \end{aligned}$$

*(quintiles)*



**Figure 10.8: Univariate model i) coefficients and ii) incidence rate ratios: deprivation quintiles (full-sample)**

Deprivation was also fitted univariately to the Poisson model as population-weighted quintiles to test for non-linearity of association. The equation above and Figure 10.8 demonstrates support for the extent of this non-linearity, with rates of detection much higher in the more deprived quintiles (quintile 1 = least deprived; quintile 5 = most deprived). Only the rate of detection in quintile 2 was not significantly different, as the 95% confidence intervals for quintiles 3, 4 and 5 were all well above the baseline. Thus, we can say that the rate of HCV detection in the most deprived quintile (5) is 8.4 times higher than quintile 1 (IRR: 8.407). Furthermore, the 95% confidence intervals for quintiles 3, 4 and 5 did not overlap, indicating that the detection rates were statistically significant not only from quintile 1, but also from each other: a dose-response effect.

## 5.5.5 Travel-time to primary healthcare

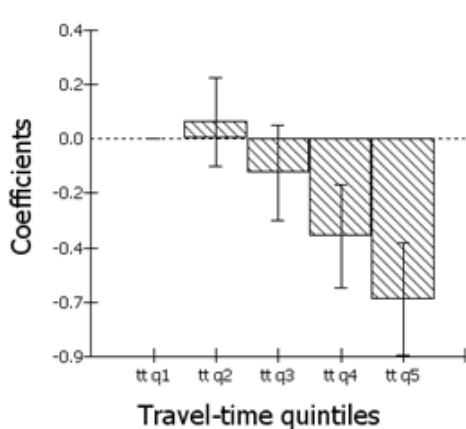
$$hcvtot_i \sim \text{Poisson}(\pi_i)$$

$$\log(\pi_i) = \text{logpoptot}_i + -5.713(0.049)\text{cons} + -0.261(0.038)\text{loggptt}$$

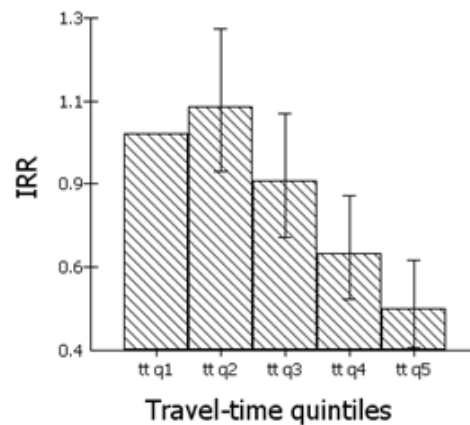
Finally, the last univariate association to test was travel-time to primary healthcare. Like the previous models of fitting deprivation as a continuous, and then as quintiles, the same applies here. First, the travel-time coefficient was negative (-0.261) and with a low standard error indicating that a statistically significant association with HCV detection ( $p = <0.001$ ). A one unit increase in travel-time was associated with a one-unit decrease in the detection rate.

$$hcvtot_i \sim \text{Poisson}(\pi_i)$$

$$\log(\pi_i) = \text{logpoptot}_i + -5.801(0.068)\text{cons} + 0.072(0.094)\text{tt q2} + -0.142(0.100)\text{tt q3}_i + -0.402(0.108)\text{tt q4}_i + -0.662(0.117)\text{tt q5}_i$$



i) Parameter with 95% confidence intervals



ii) Incidence rate ratios with 95% confidence intervals

Figure 10.9: Univariate model i) coefficients and ii) incidence rate ratios: travel-time to primary healthcare quintiles (full-sample)

Formatted and fitted as quintiles, the equation shows reasonably consistent negative coefficients, though not all with low standard errors. Assessed graphically (Figure 10.9), lower rates of HCV detection amongst populations with longer to travel are clear, particularly for quintile 4 (IRR: 0.669) and quintile 5 (IRR: 0.516), both of which were statistically significant below the 0.001 level. However, for travel-time to the nearest

primary healthcare provider, there does not appear to be a dose-response association as the 95% confidence intervals overlap for each parameter.

## **5.6 Multivariate associations (full-sample)**

Univariate Poisson models of each explanatory variable resulted in associations broadly expected with HCV detection, that is, higher rates for men relative to women, higher in young to middle-aged individuals but lower amongst the older group, higher amongst more deprived populations, and lower for those with poorer geographic access to primary healthcare. Now the question is whether these associations stay consistent in a fully adjusted model, with special interest paid towards the travel-time parameters.

Next, we begin to fit the full Poisson model, adding in each explanatory variable sequentially (Table 10.1). Model 1 illustrates the coefficient, standard error and p-value for the sex binary variable as shown earlier. To the bottom of the table a series of statistics are shown: the Pseudo R<sup>2</sup>; the log likelihood; the likelihood ratio chi square test (LR chi<sup>2</sup>); and the Prob>chi<sup>2</sup>. The Pseudo R<sup>2</sup> is an attempt to show the amount of variation explained by explanatory variables within the model. The log likelihood is used in the calculation of the LR chi<sup>2</sup>, which itself denotes whether all the explanatory variables coefficients in the Poisson model are simultaneously zero. The Prob>chi<sup>2</sup>



score is the probability of getting an LR chi2 test similar to the null hypothesis, when all coefficients would be zero. The very small p-value (<0.001) for Model 1 suggests that the parameter for sex would be significantly non-zero, which is correct (coef: 1.019).

Model 2 demonstrates the multivariate Poisson for sex and age group fitted simultaneously. Similar directions of association and significance levels are found for each age group to those in the univariate model. The coefficient for men is slightly attenuated (coef: 0.993). Model 3 introduces the main explanatory test variable, travel-time, which when formatted continuously is highly significant (p-value: <0.001) and negatively associated as before (coef: -0.246). Minimal change to the age and sex coefficients occurs, with no significant amendment to p-values. Controlling for deprivation in Model 4, also as a continuous variable, we find the strong positive and highly significant association with HCV detection (coef: 0.217; p-value: <0.001). Notably, the travel-time coefficient is still highly significant (p-value: <0.001), but also substantially attenuated to almost half the previous score. In addition, some of the age group coefficients are changed, with an increase for men and individuals between 30-34 and 35-39, but a drop for those over 40 years old.

So, after adjusting for confounders that we know might influence geographic access to healthcare, the travel-time association with HCV detection in NHS Tayside continued to be significant, but quite attenuated. As seen in the univariate analyses, Carstairs deprivation formatted as population-weighted quintiles bore a dose-response

association with detection, meaning that levels of detection were significantly higher amongst more deprived populations. Model 5 substituted the continuous measure of deprivation for the quintiles to explore whether similar affects on the travel-time coefficient would be observed. As expected, the positive association with deprivation quintiles was clear. Also notable, however, was the continued attenuation of the travel-time coefficient (coef: -0.104; p-value: 0.009) and now its significance level. Only minor changes occurred to the age and sex coefficients.

Finally, in Model 6 we substitute the continuous measure of travel-time for the quintiles as used in the univariate model, keeping the deprivation quintiles used in Model 5. It is plain that the association between HCV detection and travel-time is less strong than previously observed, with only quintile 5 statistically significant below the 0.05 level (p-value: 0.040). The full extent of this attenuation (from the initial univariate Poisson model) is evident in Figure 10.10.

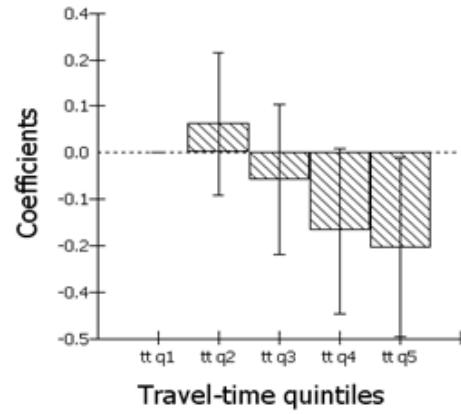
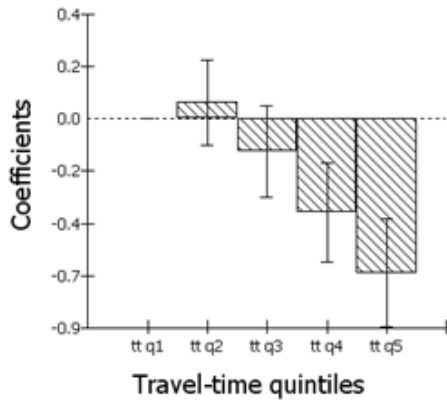
Table 10.1: Multivariate Poisson regression model: model 6 is the fully adjusted version (equation also shown)

$$\begin{aligned} \text{hcvrtot}_i \sim \text{Poisson}(\mu_i) \\ \log(\mu_i) = & \log\text{photo}_i + -7.976(0.188)\text{cons} + 1.014(0.074)\text{rmen} + 1.161(0.121)25\text{-}29_i + 1.234(0.118)30\text{-}34_i + 0.932(0.124)35\text{-}39_i + -0.306(0.115)40\text{+}_i + 0.075(0.189)\text{deprq}_2_i + 0.607(0.167)\text{deprq}_3_i + \\ & 1.290(0.154)\text{deprq}_4_i + 1.970(0.147)\text{deprq}_5_i + 0.075(0.095)\text{tt q}_2_i + -0.070(0.100)\text{tt q}_3_i + -0.201(0.108)\text{tt q}_4_i + -0.244(0.119)\text{tt q}_5_i \end{aligned}$$

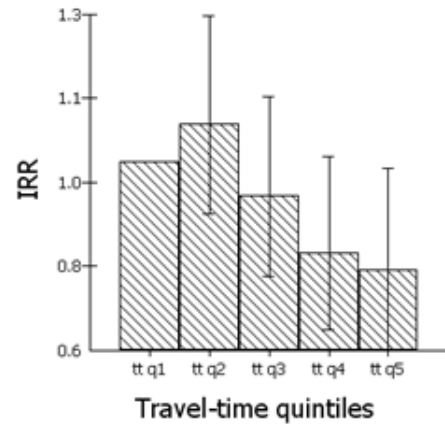
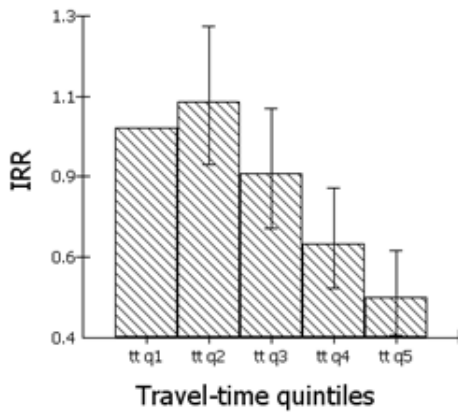
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6													
	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value	Coefficient												
Constant	-6.603	0.063	<0.001	-6.847	0.110	<0.001	-6.595	0.115	<0.001	-7.005	0.119	<0.001	-7.946	0.183	<0.001	-7.976	0.188	<0.001	
Sex ( <i>base: women</i> )																			
men	1.019	0.074	<0.001	0.993	0.074	<0.001	0.984	0.074	<0.001	1.017	0.074	<0.001	1.015	0.074	<0.001	1.014	0.074	<0.001	
Age ( <i>base: 15-24</i> )																			
25-29	1.170	0.121	<0.001	1.164	0.121	<0.001	1.159	0.121	<0.001	1.159	0.121	<0.001	1.160	0.121	<0.001	1.161	0.121	<0.001	
30-34	1.169	0.118	<0.001	1.178	0.118	<0.001	1.178	0.118	<0.001	1.220	0.118	<0.001	1.230	0.118	<0.001	1.234	0.118	<0.001	
35-39	0.805	0.124	<0.001	0.825	0.124	<0.001	0.825	0.124	<0.001	0.919	0.124	<0.001	0.930	0.124	<0.001	0.932	0.124	<0.001	
40+	-0.476	0.115	<0.001	-0.457	0.115	<0.001	-0.457	0.115	<0.001	-0.304	0.115	0.008	-0.307	0.115	0.008	-0.306	0.115	0.008	
Travel-time ( <i>log</i> )																			
Travel-time				-0.246	0.037	<0.001	-0.246	0.037	<0.001	-0.154	0.039	<0.001	-0.104	0.040	0.009				
Deprivation																			
Deprivation				0.217	0.009	<0.001													
Deprivation quintiles ( <i>base: quintile 1</i> )																			
Quintile 2										0.074	0.189	0.694	0.074	0.189	0.694	0.075	0.189	0.693	
Quintile 3										0.618	0.167	<0.001	0.618	0.167	<0.001	0.607	0.167	<0.001	
Quintile 4										1.304	0.154	<0.001	1.304	0.154	<0.001	1.290	0.154	<0.001	
Quintile 5										1.985	0.147	<0.001	1.985	0.147	<0.001	1.970	0.147	<0.001	
Travel-time quintiles ( <i>base: quintile 1</i> )																			
Quintile 2																0.075	0.095	0.428	
Quintile 3																-0.070	0.100	0.486	
Quintile 4																-0.201	0.108	0.063	
Quintile 5																-0.244	0.119	0.040	
N (observations)	33800			33800			33800			33800			33800			33800			
n (HCV diagnoses)	890			890			890			890			890			890			
Pseudo R2	0.024			0.077			0.138			0.136			0.136			0.136			
Log likelihood	-4229.613			-3981.049			-3738.512			-3746.393			-3744.026			-3744.026			
LR chi2	210.030			707.160			1192.240			1176.470			1181.210			1181.210			
Prob > chi2	<0.001			<0.001			<0.001			<0.001			<0.001			<0.001			

a) Univariate

b) Fully adjusted



i) Parameter with 95% confidence intervals



ii) Incidence rate ratios with 95% confidence intervals

Figure 10.10: i) coefficients and ii) incidence rate ratios: travel-time to primary healthcare quintiles (full-sample, (a) univariate and (b) fully-adjusted Poisson models)

## **5.7 Univariate associations (OST/non-OST stratified samples)**

### **5.7.1 Introduction**

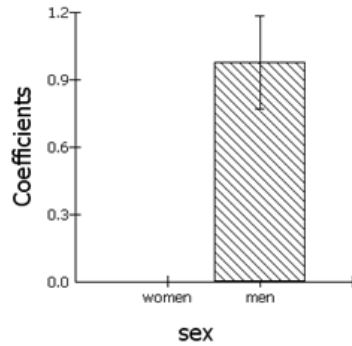
The previous analysis explored the extent to which lower rates of HCV detection were associated with poorer levels of geographic access to primary healthcare. After full adjustment for age, sex and a measure of socioeconomic deprivation, travel-time was still negatively associated with detection, albeit far weaker coefficient than initially observed. As previously discussed, the second stage of analyses is to repeat the previous steps for two separate response variables: i) age-sex-Output Area specific counts of detected patients with a history of OST; and without a history of OST. Noteworthy points for this section are that the models, graphs and tables for each sample are presented simultaneously to enable comparison. Secondly, as the models are calculated separately, direct comparisons of the magnitude of parameters would not be valid. However, general comparison of the parameter directions and relative levels of magnitude and statistical significance are feasible. Third, as much of the description earlier with regards to notation and interpretation (e.g. confidence intervals and dose-response association), commentary of these results will be deliberately more concise. As before, univariate associations are explored and then a full Poisson model fitted.

## 5.7.2 Sex

OST

$$\text{ost}_i \sim \text{Poisson}(\pi_i)$$

$$\log(\pi_i) = \text{logpoptot}_i + -7.324(0.090)\text{cons} + 0.977(0.107)\text{men}$$

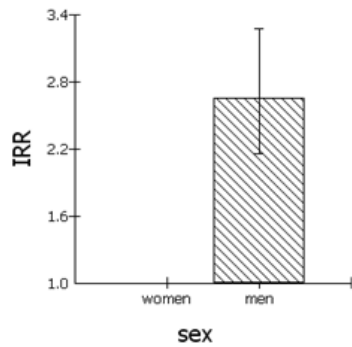
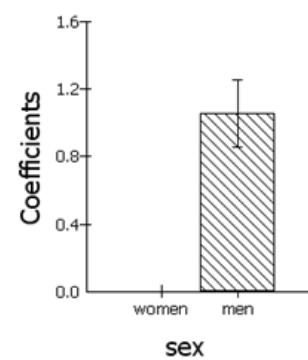


i) Parameter with 95% confidence intervals

Non-OST

$$\text{non-ost}_i \sim \text{Poisson}(\pi_i)$$

$$\log(\pi_i) = \text{logpoptot}_i + -7.268(0.088)\text{cons} + 1.057(0.103)\text{men}$$



ii) Incidence rate ratios with 95% confidence intervals

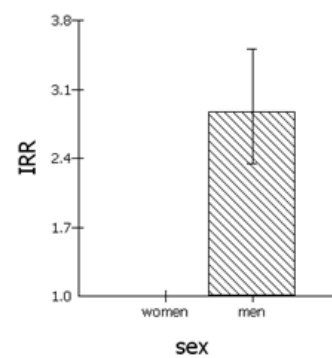


Figure 10.11: Univariate associations i) coefficients and ii) incidence rate ratios: sex (OST and non-OST-sample)

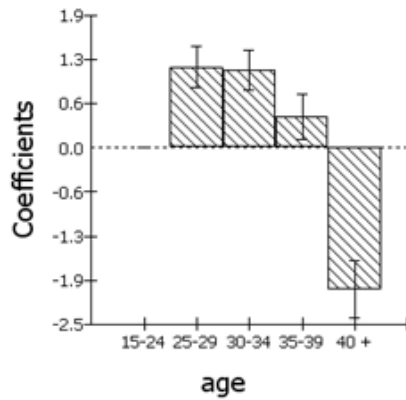
The parameter for men is positive in both models (both p-values <0.001), suggesting that rates of HCV detection are greater for men than women even after accounting for the distribution of the population.

By ways of confirmation, graphical interpretation of the coefficients and incidence rate ratios (Figure 10.11) indicate that rates of HCV detection are 2.7 times greater for men than women in the OST sample (IRR: 2.657) and 2.9 times in the non-OST sample (IRR: 2.878).

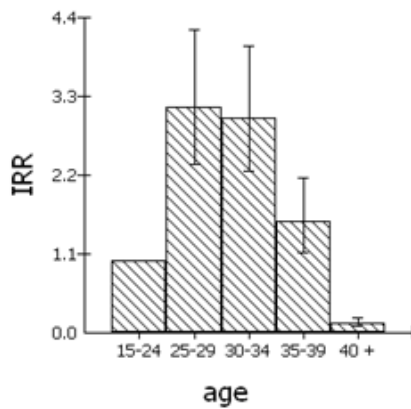
### 5.7.3 Age group

#### OST

$$\begin{aligned} \text{ost}_i &\sim \text{Poisson}(\pi_i) \\ \log(\pi_i) &= \text{logpoptot}_i + -6.658(0.119)\text{cons} + 1.147(0.151)25-29 + \\ &\quad 1.098(0.148)30-34_i + 0.439(0.167)35-39_i + -2.007(0.207)40+_i \end{aligned}$$



i) Parameter with 95% confidence intervals



ii) Incidence rate ratios with 95% confidence intervals

#### Non-OST

$$\begin{aligned} \text{non-ost}_i &\sim \text{Poisson}(\pi_i) \\ \log(\pi_i) &= \text{logpoptot}_i + -7.257(0.160)\text{cons} + 1.167(0.203)25-29 + \\ &\quad 1.205(0.197)30-34_i + 1.204(0.193)35-39_i + 0.355(0.175)40+_i \end{aligned}$$

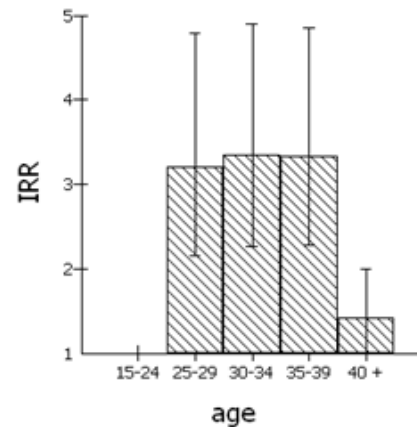
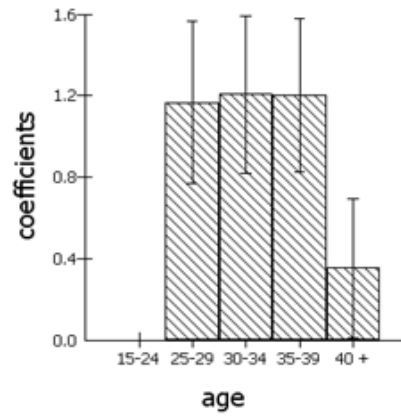


Figure 10.12: Univariate associations i) coefficients and ii) incidence rate ratios: age group (OST and non-OST-sample)

Univariate models for age show similar trends of association between OST and non-OST samples. A major difference, however, is seen in the over 40s age group, of which the OST coefficient is negative (IRR: 0.134) to the positive non-OST equivalent (IRR: 1.426). The latter, however, is marginally within the 0.05 significance level (p-value: 0.042), whereas all other coefficients in both samples are comfortably significant.

## 5.7.4 Deprivation

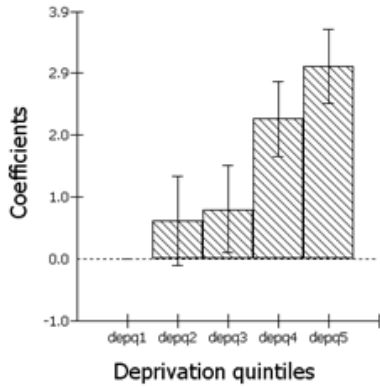
### OST

$$\text{ost}_i \sim \text{Poisson}(\mu_i)$$

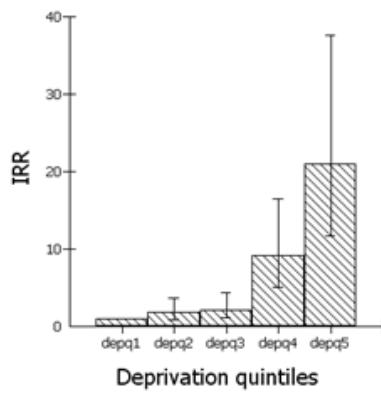
$$\log(\mu_i) = \text{logpoptot}_i + -7.090(0.061)\text{cons} + 0.276(0.012)\text{carstairs}$$

$$\text{ost}_i \sim \text{Poisson}(\mu_i)$$

$$\log(\mu_i) = \text{logpoptot}_i + -8.677(0.288)\text{cons} + 0.595(0.358)\text{depq2} + 0.783(0.346)\text{depq3}_i + 2.208(0.303)\text{depq4}_i + 3.037(0.295)\text{depq5}_i$$



i) Parameter with 95% confidence intervals



ii) Incidence rate ratios with 95% confidence intervals

### Non-OST

$$\text{non-ost}_i \sim \text{Poisson}(\mu_i)$$

$$\log(\mu_i) = \text{logpoptot}_i + -6.756(0.051)\text{cons} + 0.182(0.013)\text{carstairs}$$

$$\text{non-ost}_i \sim \text{Poisson}(\mu_i)$$

$$\log(\mu_i) = \text{logpoptot}_i + -7.448(0.156)\text{cons} + -0.087(0.225)\text{depq2} + 0.701(0.190)\text{depq3}_i + 0.989(0.182)\text{depq4}_i + 1.561(0.172)\text{depq5}_i$$

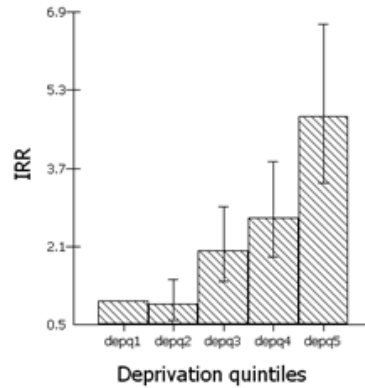
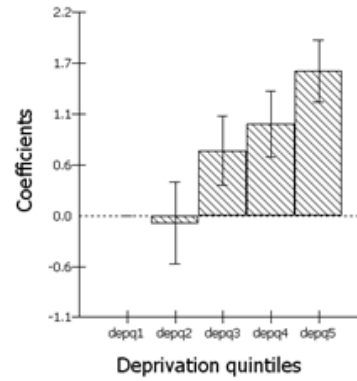


Figure 10.13: Univariate associations i) coefficients and ii) incidence rate ratios: deprivation (OST and non-OST-sample)

Similar to that seen in the full-sample, deprivation is positively associated with detection for both patients with (coef: 0.276) and without (coef: 0.182) a history of OST. The stronger coefficient in the OST sample was expected from the descriptive statistics



presented earlier. Expressed as quintiles, strong gradients were again highly significant, especially for OST, though not as dose-responses.

## 5.7.5 Travel-time to primary healthcare

### OST

$$\begin{aligned} \text{ost}_i &\sim \text{Poisson}(\pi_i) \\ \log(\pi_i) &= \text{logpoptot}_i + -6.363(0.068)\text{cons} + -0.369(0.053)\text{loggptt} \end{aligned}$$

### Non-OST

$$\begin{aligned} \text{non-ost}_i &\sim \text{Poisson}(\pi_i) \\ \log(\pi_i) &= \text{logpoptot}_i + -6.454(0.072)\text{cons} + -0.159(0.053)\text{loggptt} \end{aligned}$$

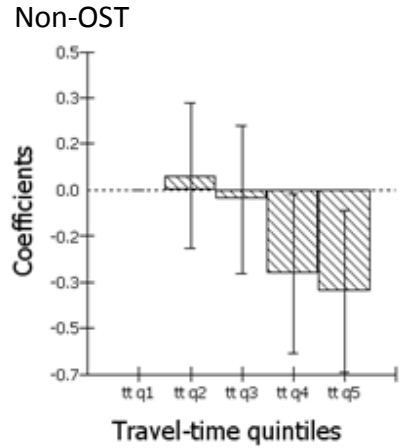
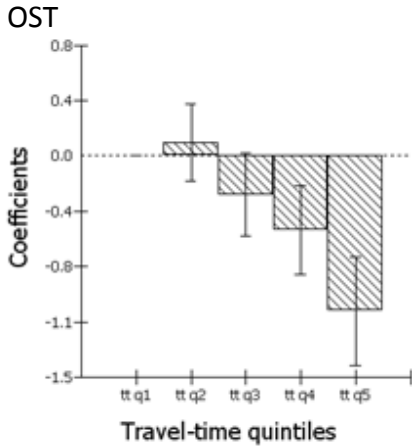
The association between travel-time and detection is mixed. Both coefficients when travel-time is expressed in continuous format are highly significant, though that for the OST sample is twice the magnitude of the non-OST. In quintile format, although negative coefficients are obtained from both samples, significance levels vary. Only quintiles 4 and 5 for each sample are statistically significant from quintile 1, suggesting that travel-time may only have some effect on reducing rates of detection amongst those that live furthest away from primary healthcare.

### OST

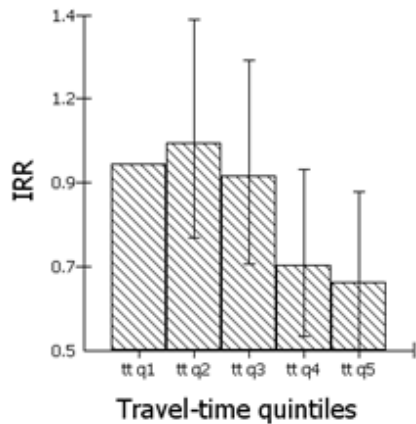
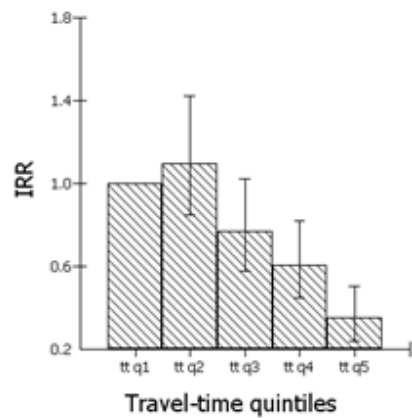
$$\begin{aligned} \text{ost}_i &\sim \text{Poisson}(\pi_i) \\ \log(\pi_i) &= \text{logpoptot}_i + -6.476(0.095)\text{cons} + 0.092(0.132)\text{tt q2} + \\ &\quad -0.261(0.144)\text{tt q3}_i + -0.501(0.155)\text{tt q4}_i + -1.050(0.188)\text{tt q5}_i \end{aligned}$$

### Non-OST

$$\begin{aligned} \text{non-ost}_i &\sim \text{Poisson}(\pi_i) \\ \log(\pi_i) &= \text{logpoptot}_i + -6.512(0.097)\text{cons} + 0.050(0.135)\text{tt q2} + \\ &\quad -0.032(0.138)\text{tt q3}_i + -0.310(0.149)\text{tt q4}_i + -0.374(0.152)\text{tt q5}_i \end{aligned}$$



i) Parameter with 95% confidence intervals



ii) Incidence rate ratios with 95% confidence intervals

Figure 10.14: Univariate associations i) coefficients and ii) incidence rate ratios: travel-time (OST and non-OST-sample)

## 5.8 Multivariate associations (OST sample)

Again, fairly consistent associations were found in univariate Poisson models. Now the consistency of these observations are tested in a fully adjusted Poisson model, adding in each explanatory variable sequentially (Table 10.2). Model 7 illustrates the highly significant association for HCV detection in men (coef: 0.977) relative to women.

Adding in the age group categorical variable in Model 8 slightly attenuates the coefficient for men (coef: 0.927), retaining its high significance. Age group coefficients are also highly significant and all positive, but for the over 40s for whom a strong negative association is evident (coef: -1.962). In Model 9, travel-time (continuous) is highly significant and negatively associated with HCV detection (coef: -0.334), though this is significantly attenuated (coef:-0.254) in Model 10 with the addition of the deprivation (continuous) control variable, itself highly significant (coef: -0.257; p-value: <0.001).

Further adjustment using deprivation quintiles in Model 11 brought more attenuation not only to the travel-time association (-0.171) but also to the statistical significance of the coefficient (p-value: 0.003). Finally, substituting the continuous measure of travel-time for quintiles (Model 12) shows that HCV detection was only significantly worse amongst those individuals with the furthest to travel (coef: -0.482; p-value: 0.011) relative to those with favourable geographic access to primary healthcare. The full extent of the adjustment for covariates on the association between detection and travel-time quintiles is illustrated in Figure 10.15, with notably smaller coefficients and wider 95% confidence intervals.

Table 10.2: Multivariate Poisson regression model (OST sample): model 12 is the fully adjusted version (equation also shown)

$$\text{ost}_i \sim \text{Poisson}(\pi_i)$$

$$\log(\pi_i) = \log\text{pop}\text{tot}_i + 8.957(0.335)\text{cons} + 0.954(0.107)\text{men} + 1.154(0.151)25\text{-}29_i + 1.213(0.148)30\text{-}34_i + 0.623(0.167)35\text{-}39_i + -1.745(0.207)40\text{+}_i + 0.530(0.359)\text{depo}q2_i + 0.578(0.348)\text{depo}q3_i + 1.943(0.306)\text{depo}q4_i + 2.725(0.297)\text{depo}q5_i + 0.103(0.132)\text{tt}q2_i + -0.143(0.144)\text{tt}q3_i + -0.233(0.156)\text{tt}q4_i + -0.482(0.190)\text{tt}q5_i$$

	Model 7		Model 8		Model 9		Model 10		Model 11		Model 12							
	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value						
Constant	-7.324	0.090	<0.001	-7.237	0.142	<0.001	-6.904	0.149	<0.001	-7.426	0.155	<0.001	-8.909	0.328	<0.001	-8.957	0.335	<0.001
Sex (base: women)																		
men	0.977	0.107	<0.001	0.927	0.107	<0.001	0.926	0.107	<0.001	0.959	0.107	<0.001	0.955	0.107	<0.001	0.954	0.107	<0.001
Age (base: 15-24)																		
25-29	1.162	0.151	<0.001	1.153	0.151	<0.001	1.153	0.151	<0.001	1.148	0.151	<0.001	1.153	0.150	<0.001	1.154	0.151	<0.001
30-34	1.128	0.148	<0.001	1.140	0.148	<0.001	1.140	0.148	<0.001	1.186	0.148	<0.001	1.208	0.148	<0.001	1.213	0.148	<0.001
35-39	0.462	0.167	0.006	0.488	0.167	0.004	0.488	0.167	0.004	0.598	0.167	<0.001	0.621	0.166	<0.001	0.623	0.167	<0.001
40 +	-1.962	0.206	<0.001	-1.937	0.206	<0.001	-1.937	0.206	<0.001	-1.752	0.207	<0.001	-1.746	0.206	<0.001	-1.745	0.207	<0.001
Travel-time (log)																		
Travel-time				-0.334	0.053	<0.001	-0.334	0.053	<0.001	-0.254	0.056	<0.001	-0.171	0.057	0.003			
Deprivation																		
Deprivation quintiles (base: quintile 1)																		
Quintile 2																		
Quintile 3																		
Quintile 4																		
Quintile 5																		
Travel-time quintiles (base: quintile 1)																		
Quintile 2																		
Quintile 3																		
Quintile 4																		
Quintile 5																		
N (observations)	33800			33800			33800			33800			33800			33800		
n (HCV diagnoses)	420			420			420			420			420			420		
Pseudo R2	0.019			0.125			0.132			0.201			0.204			0.205		
Log likelihood	-2434.465			-2171.200			-2152.139			-1981.613			-1975.222			-1975.062		
LR chi2	91.920			618.450			656.570			997.620			1010.400			1014.720		
Prob > chi2	<0.001			<0.001			<0.001			<0.001			<0.001			<0.001		

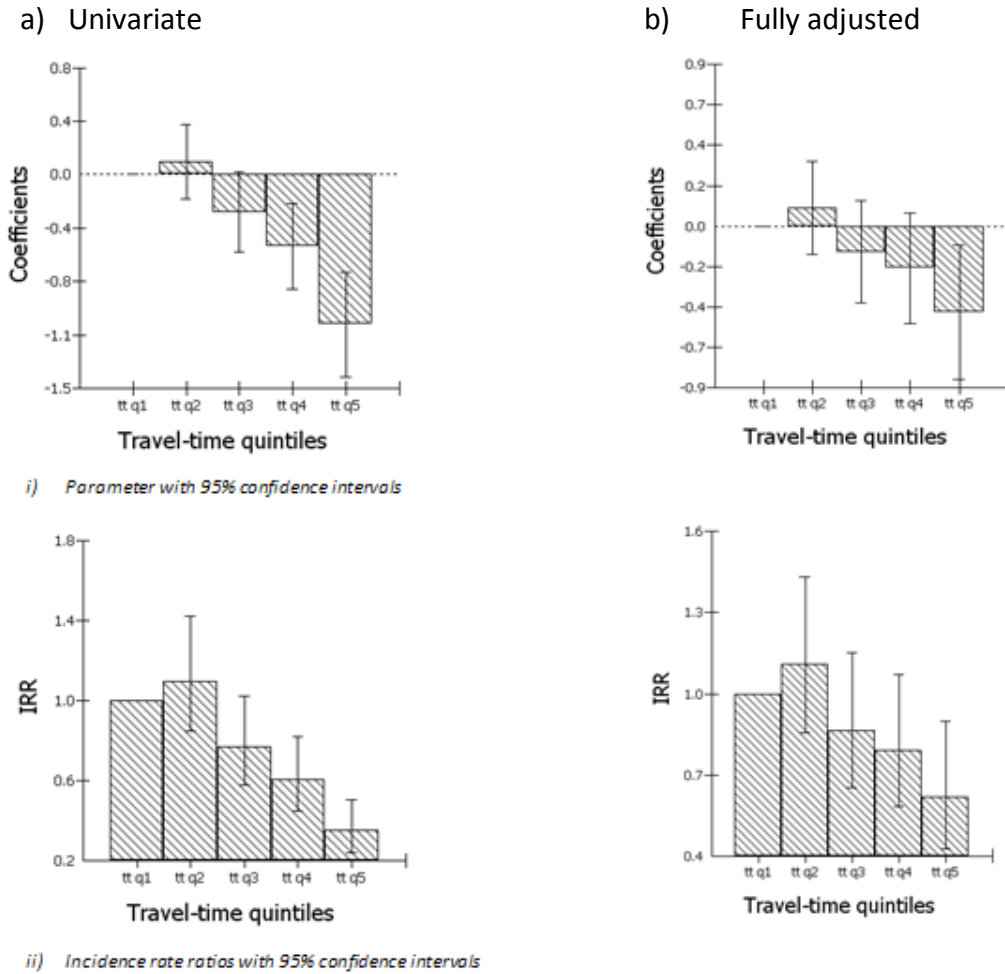


Figure 10.15: i) coefficients and ii) incidence rate ratios: travel-time to primary healthcare quintiles (OST-sample, (a) univariate and (b) fully-adjusted Poisson models)

## 5.9 Multivariate associations (non-OST sample)

Relative to the OST sample, univariate Poisson model coefficients were less consistent. Multivariate Poisson regression modelling would be a more thorough test of these associations (Table 10.3). Model 13 shows the significant coefficient for HCV detection in men (coef: 1.057) compared with women. All age groups were found to be

significantly positively associated with detection in Model 14, though with the over 40s least powerfully. The travel-time coefficient was significantly negative in Model 15 (coef: -0.162; p-value: 0.002). However, this association was highly attenuated (coef: -0.071) by the inclusion of a continuous measure of deprivation (coef: 0.179) in Model 16. Moreover, the travel-time coefficient was rendered statistically insignificant (p-value: 0.198). Sensu previous modelling, the continuous measure of deprivation was substituted for the strongly associated deprivation quintiles (Model 17) and finally the continuous travel-time for travel-time quintiles (none significant).

By way of a final confirmation, Figure 10.16 illustrates the univariate and fully adjusted travel-time quintile coefficients. Clearly, the significant associations found initially are accounted for by the other covariates, with a less-consistent gradient observed and wide 95% confidence intervals overlapping the baseline for the fully-adjusted coefficients.

**Table 10.3: Multivariate Poisson regression model (non-OST sample): model 18 is the fully adjusted version (equation also shown)**

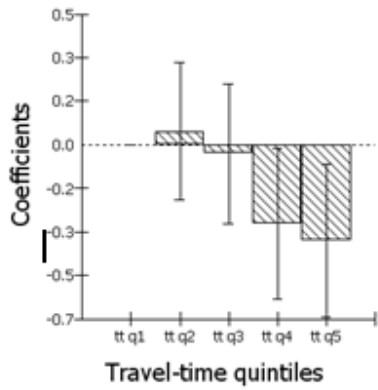
$$\text{non-ost}_i \sim \text{Poisson}(\pi_i)$$

$$\log(\pi_i) = \text{logoptot}_i + -8.780(0.254)\text{cons} + 1.069(0.103)\text{men} + 1.173(0.202)25-29_i + 1.286(0.194)35-39_i + 0.536(0.175)40+ + -0.105(0.226)\text{deprq}_2 + 0.658(0.191)\text{deprq}_3 + 0.963(0.185)\text{deprq}_4 + 1.526(0.174)\text{deprq}_5 + 0.046(0.136)\text{tt q}_2 + 0.002(0.138)\text{tt q}_3 + -0.166(0.150)\text{tt q}_4 + -0.077(0.155)\text{tt q}_5;$$

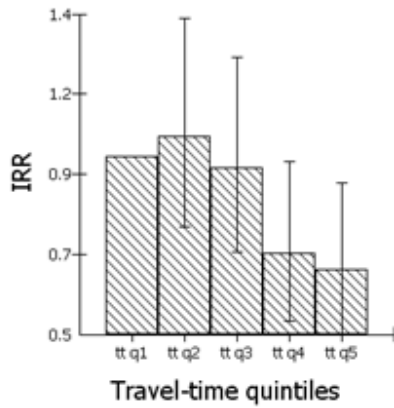
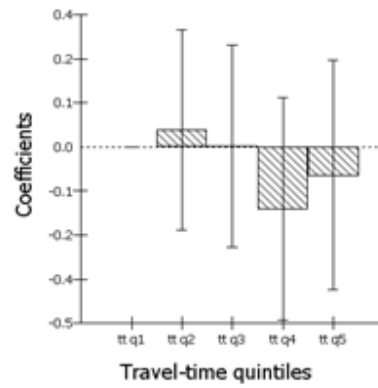
	Model 13	Model 14	Model 15	Model 16	Model 17	Model 18													
	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value													
Constant	-7.268	0.088	<0.001	-7.928	0.178	<0.001	-7.758	0.185	<0.001	-8.070	0.189	<0.001	-8.778	0.247	<0.001	-8.780	0.254	<0.001	
Sex (base: women)																			
men	1.057	0.103	<0.001	1.052	0.103	<0.001	1.054	0.103	<0.001	1.070	0.103	<0.001	1.069	0.103	<0.001	1.069	0.103	<0.001	
Age (base: 15-24)																			
25-29				1.184	0.202	<0.001	1.180	0.203	<0.001	1.175	0.202	<0.001	1.173	0.202	<0.001	1.173	0.203	<0.001	
30-34				1.238	0.196	<0.001	1.244	0.197	<0.001	1.281	0.196	<0.001	1.283	0.196	<0.001	1.286	0.197	<0.001	
35-39				1.230	0.193	<0.001	1.243	0.193	<0.001	1.321	0.193	<0.001	1.325	0.193	<0.001	1.326	0.194	<0.001	
40+				0.405	0.175	0.020	0.417	0.175	0.017	0.540	0.175	0.002	0.535	0.175	0.002	0.536	0.175	0.002	
Travel-time (log)							-0.162	0.052	0.002	-0.071	0.055	0.198	-0.040	0.056	0.473				
Deprivation							0.179	0.013	<0.001										
Deprivation quintiles (base: quintile 1)																			
Quintile 2																			
Quintile 3																			
Quintile 4																			
Quintile 5																			
Travel-time quintiles (base: quintile 1)																			
Quintile 2																			
Quintile 3																			
Quintile 4																			
Quintile 5																			
N (observations)	33800			33800			33800			33800			33800			33800			
n (HCV diagnoses)	470			470			470			470			470			470			
Pseudo R2	0.024			0.046			0.079			0.078			0.078			0.078			
Log likelihood	-2389.064			-2341.360			-2336.684			-2257.435			-2256.474			-2256.474			
LR chi2	118.400			213.810			386.370			381.660			383.580			383.580			
Prob > chi2	<0.001			<0.001			<0.001			<0.001			<0.001			<0.001			

a) Univariate

b) Fully adjusted



i) Parameter with 95% confidence intervals



ii) Incidence rate ratios with 95% confidence intervals

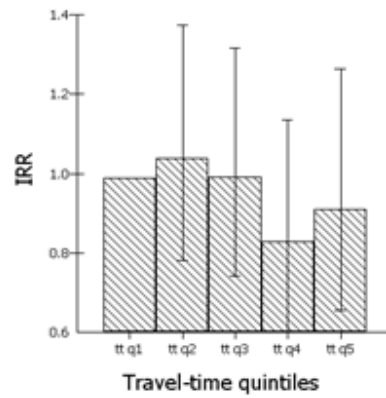


Figure 10.16: i) coefficients and ii) incidence rate ratios: travel-time to primary healthcare quintiles (non-OST-sample, (a) univariate and (b) fully-adjusted Poisson models)



## 5.10 Discussion

In response to (Monnet et al. 2006; Monnet et al. 2008), this study set out to test the association of HCV detection and geographic access to primary healthcare in Tayside, Scotland. In a previous chapter I suggested that although there are several hypotheses why detection rates may be lower amongst populations required to travel further to their nearest GP, a lack of appropriate control for the prevalence of risk factors for HCV is likely to bias the results found in France. The principal finding of this chapter, in contrast to the studies by Monnet and colleagues, is the demonstration that the effect of travel-time on detection is significantly reduced after adjusting for small-scale measures of socioeconomic deprivation (a surrogate marker for risk factor prevalence). Moreover, the significance level for travel-time was negated in several instances below the 0.95% level after controlling for deprivation. Only for the OST group was there a persisting influence of travel-time of statistical significance (when controlling for the Carstairs deprivation index). In consideration of our other findings and that HCV prevalence is very likely to be concentrated into urban areas with short travel-times to a GP, we suggest that selection bias is probably causing the significant decay effect as the Carstairs index is a widely validated measure of socioeconomic deprivation, but only associated with some of the risk factors of HCV infection (e.g. IDU).

On this evidence, we strongly suggest that the models published by Monnet and colleagues (2006; 2008) were sub-optimal in their control for the expected spatial

variation of HCV prevalence and that their subsequent results should be viewed with caution. Without adjusting for socioeconomic deprivation at a small geographic scale, it is likely their ecological study suffers selection bias and we cannot be sure whether the distance-decay effect reported in France is an issue in reality, or mere statistical artefact. A conservative estimate based on the substantial influence of socioeconomic deprivation in our study suggests that the magnitude of the distance-decay trend in France would at least be significantly attenuated.

Our analyses of associations between travel-time and HCV detection used a robust and well validated modelling approach. However, our study does have some limitations. OST is an indicator of previous IDU, though there will be some people with a history of IDU that have not had OST. It was impossible to distinguish between patients in this group that were infected through IDU and those infected iatrogenically, though this indicator was primarily used to shed light on general trends in detection associated with IDU and socioeconomic deprivation. This indicator helped to identify a non-effect of travel-time on the detection of the more heterogeneous non-OST group, whilst the only significant effect was for those with a history of OST of whom are expected to be more spatially concentrated into more deprived, inner-city areas. In the absence of data pertaining directly to IDU, this was the best available alternative and it is likely that had information on injecting practices been available, a much steeper gradient of association with deprivation would probably have been observed.

The Carstairs deprivation score and our travel-time estimates were both calculated for Output Areas and are prone to the ecological fallacy (Schwartz 1994) and it is possible that deprived people in the more rural, remote areas are hidden (Haynes and Gale 2000) by the larger size of the spatial units (which are partially based on minimum population thresholds to ensure comparability and anonymity). Our use of Output Areas, as the smallest geographic unit at which census information is disseminated represents the most optimal solution to control for issues associated with social heterogeneity.

More detailed estimates of travel-time, incorporating data on public transport availability, frequency and expense may have provided a better overall portrayal of geographic access (Lovett, Haynes, Sunnenberg, and Gale 2002; Martin, Wrigley, Barnett, and Roderick 2002), though such advanced indicators are seldom utilised in studies of this genre and there is still an ongoing debate more generally of whether GIS-determined measures are an appropriate substitute for perceived accessibility (Haynes, Jones, Sauerzapf, and Zhao 2006; Macintyre, Macdonald, and Ellaway 2008b). Finally, the absence of negative test records and detailed, reliable, HCV data from other NHS boards restricted the applicable methodology and study population to NHS Tayside. The emergence of such data available for the whole of Scotland is needed to test for replication and to extend this thesis with increasingly sophisticated study design.

## **5.11 Summary**

### **5.11.1 What we knew before?**

Detection rates of HCV in Scotland are low. Social factors may be contributing to this shortfall. In particular, individuals lacking geographic access to healthcare may play a particularly important role, such is the extent of topography and infrastructure exacerbating the remoteness of some rural communities.

### **5.11.2 What this study has contributed?**

This study has contributed original findings in two regards: i) the first study of geographic access and HCV detection in Scotland; ii) an extension of the France-based studies using a widely validated measure of socioeconomic deprivation and innovative use of patient OST records to identify a group highly likely to have been infected with HCV through IDU. Although travel-time did appear to be associated with detection, on closer inspection this trend persisted only for those individuals with a history of OST. The absence of a significant effect for the non-OST sample suggests that this trend, and quite possibly those published by Monnet and colleagues, are an artefact of selection bias.

### **5.11.3 What gaps remain?**

Although in this particular case study, poor geographic access to primary healthcare does not appear to hinder HCV detection, this may not be the case in other parts of Scotland. Further research is required to replicate this study in other regions, incorporating individual measures of socioeconomic position.

# **6. Are the chances of referral poorer for individuals lacking geographic access to an HCV specialist centre?**

## **6.1 Introduction**

Referral to specialist healthcare, as has been previously discussed, is by no means certain for those individuals that medically require it. Various studies have explored trends of referral outcomes by GPs, but findings have been sporadic and inconsistent. Nevertheless, national guidelines (Scottish Intercollegiate Guidelines Network 2006) state that referral to HCV specialist healthcare in Scotland should be the case for all individuals chronically infected with HCV. But not everybody diagnosed with HCV gets referred, and there is little information in the Scotland-based context as to why this might be.

Various social factors have been posited, such as a lack of GP awareness of HCV infection and clinical protocol (d'Souza et al. 2004; Ouzan et al. 2003a; Ouzan et al. 2003b; Rotily et al. 2002; Shehab, Sonnad, and Lok 2001). Another cause may be the widely-documented stigmatisation of individuals with a history of intravenous drug use (IDU) (Edlin et al. 2005; Paterson, Backmund, Hirsch, and Yim 2007; Watkins and Jacoby 2007; Zickmund et al. 2003), who make up a large proportion of the HCV-infected population already diagnosed in Scotland (Hutchinson, Bird, and Goldberg 2005; Hutchinson et al. 2006; Judd et al. 2005b; Roy et al. 2007). A lack of GP awareness is likely to be a major factor associated with stigma and research has shown that those in the medical profession that spend more time with individuals that have a history of IDU are less likely to discriminate (Brener, von Hippel, and Kippax 2007). Thus, in more rural, remote communities where the prevalence of IDU and HCV are both low, it could very well be the case that awareness is also low, and the risk of stigma-influences on referral much higher.

Furthermore, individuals with a history of IDU may also be less likely to be referred due to concerns over i) a perceived lack of adherence to proposed treatment; ii) the exacerbation of psychiatric diseases; iii) and reinfection (Bini et al. 2005; Edlin 2002; Edlin 2004; Edlin et al. 2005; Hallinan, Byrne, Agho, and Dore 2007; Loftis, Matthews, and Hauser 2006; Soriano 2006; Stoové, Gifford, and Dore 2005; Sylvestre, Litwin, Clements, and Gourevitch 2005). In a similar vein, GPs that have close relationships with their patients, said to be typical amongst more rural, remote communities with

limited geographic access to healthcare (Farmer et al. 2006; Farmer, Lauder, Richards, and Sharkey 2003; Higgs 1999), may be reluctant to refer patients whom are perceived to gain little from referral, or struggle with the frequent visits to see a specialist that may be quite a long way away. This reluctance may be particularly towards patients with lower levels of mobility, such as the rural elderly and those suffering poor mental health which is common amongst individuals infected with HCV (Arcury et al. 2005; Arcury, Preisser, Gesler, and Powers 2005; Chen and Yang 2002; Gohier, Goeb, Rannou-Dubas, Fouchard, Cales, and Garre 2003; Golden, O'Dwyer, and Conroy 2005).

Higgs suggested that more research is required to assess the extent to which a lack of geographic access to specialist healthcare impacts upon the GPs referral decisions (Higgs 2004). It seems that the case of HCV in Scotland presents an opportunity to do this, since whilst geography ought to not be a barrier for referral to a specialist, the hypotheses outlined above suggest that there is every possibility. In other words, chances for referral may depend not only on who the characteristics of a patient, but also where that patient lives. Hence, the aim of this chapter is to present analyses in reference to the following research questions:

1. To what extent are HCV-diagnosed patients with further to travel to a specialist centre less likely to be referred?
2. To what extent is there evidence that some patients are less likely to be referred due to a history of IDU?



## 6.2 Methodological approach

Whereas the Poisson regression method was used in the previous chapter to model rates of HCV detection, which was particularly adept at dealing with rare events, the forthcoming analyses require a different type of approach. In this chapter, the main response variable takes a binary or dichotomous format, with a study sample of individuals diagnosed with HCV that were either referred to a specialist centre, or not. Similar to the Poisson-distributed count data of the previous chapter, this binary response is not normally distributed and calls for an alternative from the Ordinary Least Squares (OLS) linear regression method.

One popular approach is the logistic regression model (Hosmer and Lemeshow 2004; Hosmer, Taber, and Lemeshow 1991). This is a method that handles a binary response variable, with associations interpreted from coefficients representing the log odds of achieving the fitted response (i.e. the log odds of being referred, as opposed to not being referred). It is common, especially in the medical research literature, to exponentiate the coefficients in a similar way to was done in the previous chapter, to enable interpretation of association in terms of odds. The exponentiated coefficient is commonly referred to as an odds ratio, which like the incidence rate ratio, is the ratio of fitted events compared to baseline (i.e. the number of patients referred, versus the number that weren't). Positive coefficients and odds ratios above 1 indicate the

increased likelihood of the fitted response occurring, whereas negative coefficients and odds ratios below 1 suggest a decreased likelihood.

## **6.3 Study specification**

### **6.3.1 Study sample and setting**

The data used in the following analyses has been described in detail in a previous chapter, but here some specifics to this chapter are outlined. The data comprises the 890 individuals diagnosed with anti-body positive HCV infection in NHS Tayside. This data is not aggregated sensu the previous chapter modelling rates per Output Area, each unit of analysis is now an individual patient. Again, all patients extracted for this study had full age, sex, and 2001 Output Area of residence information, were at least 15 years old and were not in prison. Whether a patient was referred to a specialist HCV centre or not was known by a dichotomous variable, which represented whether each individual appeared in the HCV Clinical Database held in the only HCV specialist centre available in NHS Tayside, located at Ninewells Hospital (Dundee). Patients within the ELDIT living in Output Areas outside the boundary of NHS Tayside were omitted for similar reasons to before, as other individuals diagnosed with HCV in such areas could realistically have been referred to another specialist centre within their own

healthboard. As the study setting continues to be NHS Tayside, the mixture of densely-populated and sparsely populated areas as described in the previous chapter continues to apply here.

### **6.3.2 Variable definition**

The response variable in the Logistic regression method takes the form of binary data. Thus, individuals diagnosed with HCV were either (1) referred; or (0) not referred to the specialist centre in Dundee. Sex was treated as a binary categorical variable whilst age was expressed in a continuous format. Records of history of opiate substitution therapy were linked to each patient, with identification taking the format of a binary categorical variable: (1) “yes”; or (0) “no”.

Once again the main explanatory test variable was geographical, based upon the Output Area of residence. This time, however, the measure of travel-time corresponded to the journey time between the geometric centroid of the Output Area to the specialist centre, again represented by easting and northing coordinates. The same method in terms of using average speeds and distinguishing between different types of road continues to apply. As does the interpretation, with lower travel-times indicating more favourable geographic access to specialist HCV healthcare.

Adjustment for modifying influences on geographic accessibility were essential, as previously discussed in an earlier chapter. The Carstairs index of socioeconomic deprivation was used (Carstairs and Morris 1989a) in the absence of individual-level data on employment, income or other measures of socioeconomic position. Higher scores denote greater relative disadvantage and the prevalence of risk factors.

### **6.3.3 Analysis specification**

The full sample was fitted to a binary logistic regression model, first with an exploration of univariate trends, followed by a fully adjusted model with explanatory variables added sequentially. Models were further augmented by patient history of OST to explore contrasting influences of geographic access on referral. The travel-time measure was calculated as a natural logarithm to reduce problems of skewness. Travel-time quintiles (based upon the study sample) were used to explore for non-linear effects.

## 6.4 Descriptives

Characteristic	Referred	Not referred
Number of men (%)	237 (67.7)	400 (74.1)
Number of women (%)	113 (32.3)	140 (25.9)
Mean age (years)	34.3	37.3
Number of patients with a history of OST (%)	176 (50.3)	244 (45.2)
Mean Carstairs deprivation	2.4	2.3
Mean HCV specialist centre travel (mins)	19.5	23.4
Number of patients (%)	350 (39%)	540 (61%)

**Table 11.1: Study population characteristics**

Table 11.1 summarises some of the key characteristics of the study population. 350 patients (39%) were referred to the HCV specialist centre at Ninewells Hospital, Dundee, relative to 540 (61%) that were not. Men were more common in both the referred and not referred groups, though more so in the latter (68% to 74% respectively). The mean age at which patients were diagnosed was in the mid-30s for both groups, though the mean for those not referred was slightly higher (34 to 37 respectively). Approximately half of the referred sample had a reported history of OST, whereas this was down to 45% of those going unreferred. The mean deprivation score very similar for both groups, but the mean travel-time for those unreferred was slightly longer at 23.4 minutes, compared to the 19.5 minutes for the referred group.

Figure 11.1 shows the extent of geographic access to the HCV specialist centre, illustrating the travel-time quintiles. A large number of people reside in excess of 45 minutes travel-time to the HCV specialist centre. Figure 11.2 shows that those persons with the furthest to travel tended to live in more affluent areas. Greater socioeconomic

heterogeneity was evident amongst populations located closer to the HCV specialist centre. This suggests that the most socioeconomically disadvantaged populations within NHS Tayside did not generally have the furthest to travel.

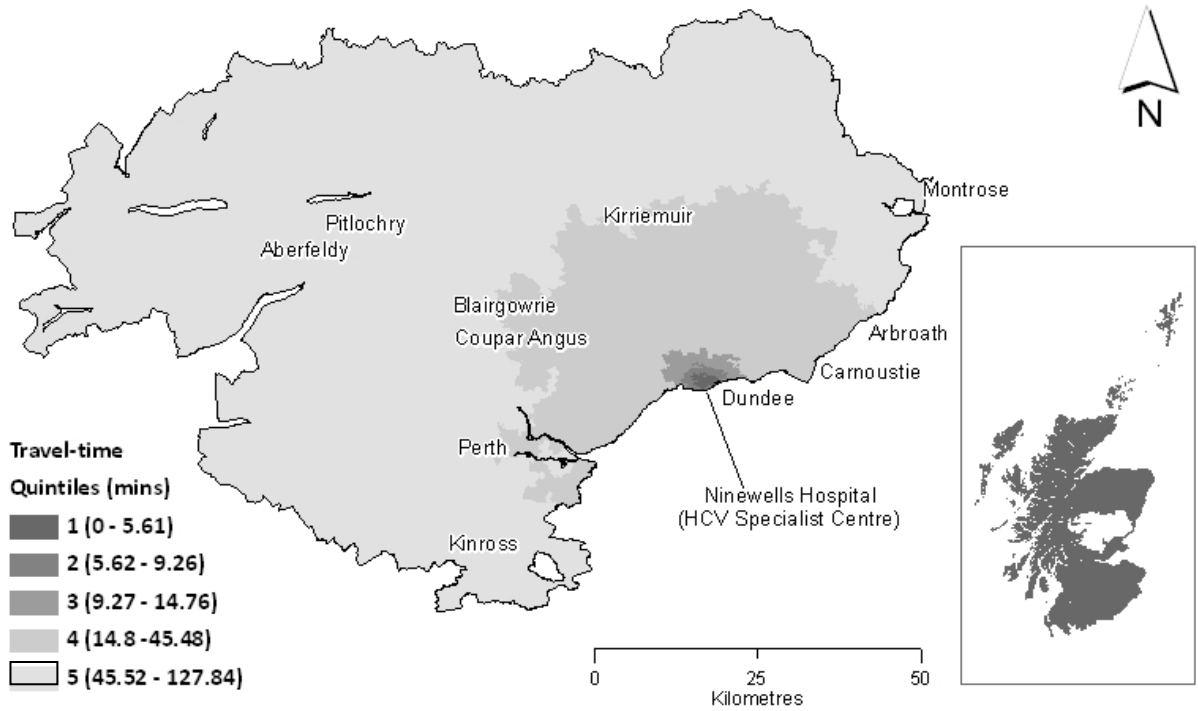


Figure 11.1: Travel-time quintiles to an HCV specialist centre in NHS Tayside

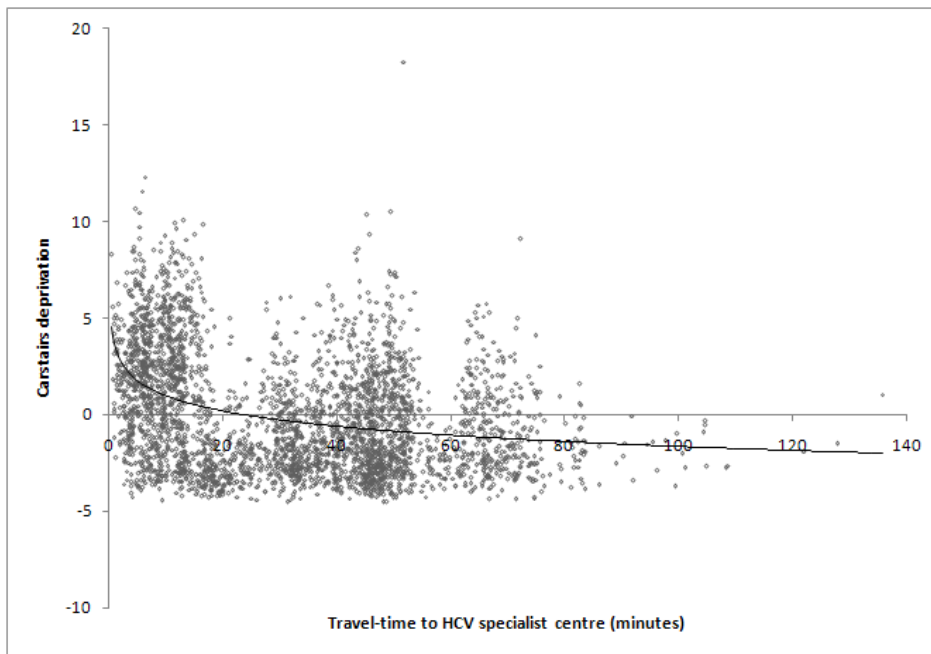
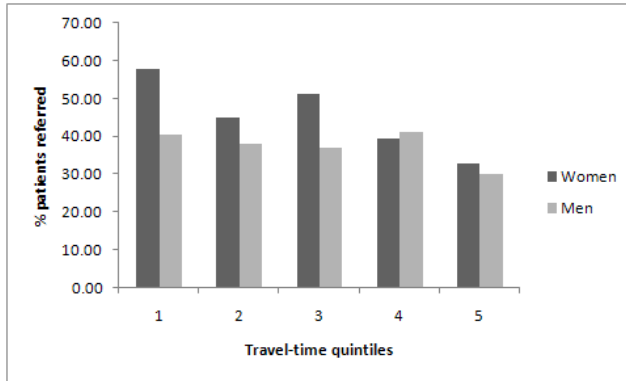
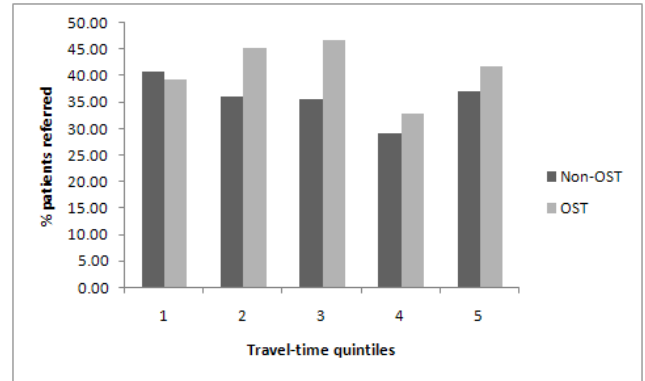


Figure 11.2: Travel-time to an HCV specialist centre and association with socioeconomic deprivation



**Figure 11.3: Travel-time to HCV specialist centre and percentage of patients referred, by sex (left)**



**Figure 11.4: Travel-time to HCV specialist centre and percentage of patients referred, by history of opiate substitution therapy (right)**

Figure 11.3 demonstrates the percentage of the detected population that were referred to the specialist centre, stratified by travel-time quintiles. It is clear that a higher percentage of patients were referred from quintile 1 (40.2% of men and 50.9% of women respectively), with most favourable geographic access to the specialist centre, in comparison to those resident furthest away in quintile 5. The steep 'gradient' is most obvious for women, though a little shallower for men. This differential is noteworthy in that it could be suggesting GPs are discriminating in their decision-making between the men and women, though it is impossible to state with certainty why this could be. Further, it does not seem to be the case that women are less likely to be referred than men, but that they are more likely to be referred when living in close proximity to the specialist, whereas chances become more equal amongst individuals with further to travel irrespective of sex.

Similar descriptive analyses for the OST and non-OST groups were less clear (Figure 11.4). For those with a history of OST, no consistent gradient was obvious, with only the percentage of patients referred in quintile 4 less than quintile 1. The percent referred amongst those without a history of OST did seem to drop with subsequent quintiles from 1 till 4, but rise up again in quintile 5. These trends could suggest that a history of OST is not a significant barrier to referral for individuals lacking geographic access to healthcare. Since the non-OST group is heterogeneous, including older patients infected through blood transfusion and having tried IDU briefly earlier in life, plus those addicted to IDU but never having received OST, it is not surprising that no clear gradient is evident in this case.

## 6.5 Univariate associations (full-sample)

### 6.5.1 Introduction

To get an initial idea of associations between response and explanatory variables, univariate Logistic regression models of referral were fitted. The notation for the null model is:

$$\begin{aligned} \text{referred}_i &\sim \text{Binomial}(\text{cons}_i, \pi_i) \\ \text{logit}(\pi_i) &= \beta_0 \text{const} \end{aligned}$$



where 'referred' denotes the full-sample of detected patients is being used as the response variable and ' $\beta_0$ ' the parameter for the model constant.

## 6.5.2 Sex

$$\text{referred}_i \sim \text{Binomial}(\text{const}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -0.214(0.126)\text{const} + -0.309(0.151)\text{Male}_i$$

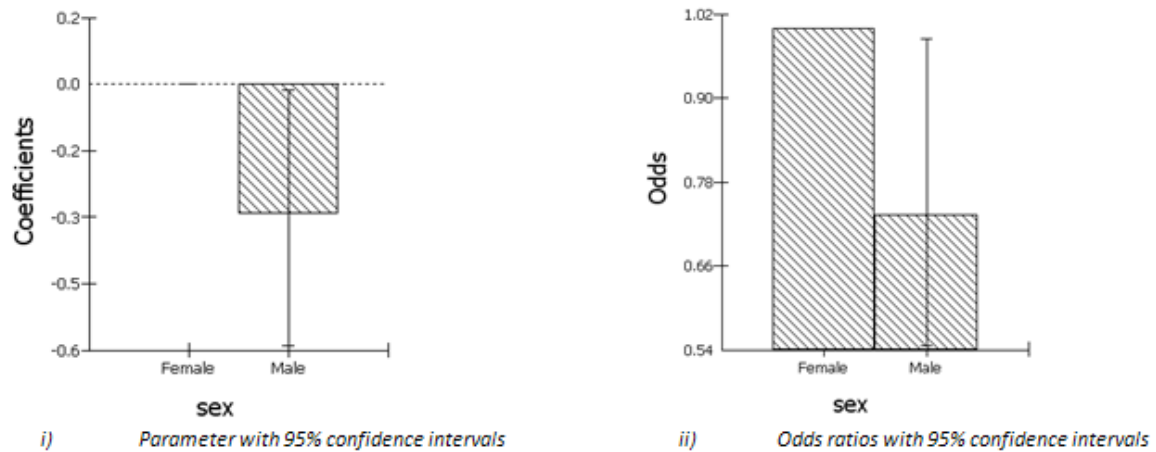


Figure 11.5: Univariate model i) coefficients and ii) incidence rate ratios: sex (full-sample)

The association between referral and sex is shown in Figure 11.5, in which women were fitted as the baseline and the coefficient for men allowed to vary. The coefficient for men shows that a one unit change in sex results in a -0.309 unit decrease in the likelihood referral, though the wide 95% confidence intervals suggest uncertainty over the magnitude of the effect (p-value: 0.040).

### 6.5.3 Age

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$
$$\text{logit}(\pi_i) = 0.273(0.218)\text{const} + -0.020(0.006)\text{age}_i$$

The univariate logistic model with age as the sole explanatory variable demonstrated negative association with referral. This meant that for every one year increase in age at the time the patient was diagnosed with HCV, the likelihood of referral diminished by -0.020 (p-value: 0.001). Older patients were less likely to be referred.

### 6.5.4 OST history

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$
$$\text{logit}(\pi_i) = -0.531(0.096)\text{const} + 0.205(0.137)\text{Yes}_i$$

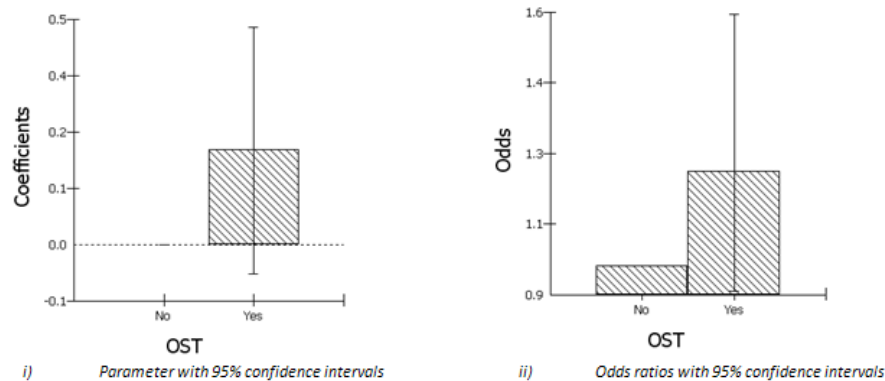


Figure 11.6: Univariate model i) coefficients and ii) incidence rate ratios: OST history (full-sample)

As was seen earlier in the descriptives, the association between referral and patient history of OST takes no clear trajectory. Although the OST sample had a coefficient of 0.205, or an odds ratio of 1.227 making them 1.2 times more likely to be referred than the non-OST sample, the association was statistically insignificant as demonstrated by

relatively large standard error (0.137) and the 95% confidence intervals overlapping baseline (p-value: 0.137).

### 6.5.5 Deprivation

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -0.451(0.086)\text{const} + 0.007(0.022)\text{carstair2}_i$$

Similar to the OST association, the univariate model with deprivation as an explanatory variable found a positive association. However, the magnitude of association was very weak (coef: 0.007; odds ratio: 1.007) suggesting little variation in the likelihood of referral by socioeconomic deprivation. Further confirmation is given by the relatively large standard error at 0.022 (p-value: 0.740).

### 6.5.6 Travel-time to specialist

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -0.062(0.178)\text{const} + -0.145(0.064)\text{loghcvtt}_i$$

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -0.213(0.150)\text{const} + -0.188(0.215)\text{ttq}_2 + -0.174(0.214)\text{ttq}_3 + -0.169(0.214)\text{ttq}_4 + -0.602(0.222)\text{ttq}_5$$

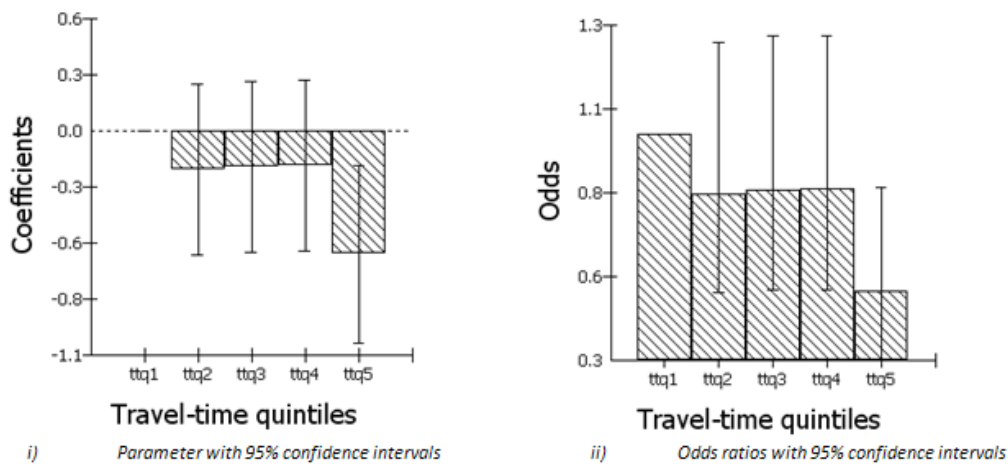


Figure 11.7: Univariate model i) coefficients and ii) incidence rate ratios: travel-time to specialist (full-sample)

For the main explanatory variable, travel-time, univariate modelling demonstrated the negative association hypothesised (coef: -0.145; p-value: 0.024). It appeared that the likelihood of referral might well diminish for individuals living further from a specialist centre. In an exploration of non-linear effects, that is, were individuals living further away several times more likely to go unreferred, the results of univariate modelling with travel-time quintiles are shown in Figure 11.7. From this model, whilst each coefficient or odds ratio of the quintiles 2-5 are all below that of quintile 1, only quintile 5 (coef: -0.602) is statistically significant (p-value: 0.007). This suggests that geographic access to specialist healthcare is not linearly associated with the likelihood of referral.

## **6.6 Multivariate associations (full-sample)**

The univariate models demonstrated some interesting findings. Referral was statistically less likely for men, older patients, and those with the furthest to travel. A history of OST and socioeconomic deprivation bore no significant association. Each of these explanatory variables were then put into a fully adjusted logistic regression model (Table 11.2) to investigate whether the aforementioned trends held constant. Model 1 showed the coefficient of men (-0.309) relative to women. Adding age to the model (2) had little effect on the sex coefficient, and itself was significantly negative (coef: -0.020). As seen in the univariate association, individuals with a history of OST (Model 3) were more likely to be referred (coef: 0.003), but not significantly so (p-value: 0.982).

Much the same in terms of (a lack of) significance was observed with the measure of socioeconomic deprivation in Model 4, but the direction of effect actually reversed (coef: -0.008). In Model 5, the main explanatory variable, travel-time to the specialist centre, was added with little change to the other covariates. The travel-time coefficient was negative (coef: -0.158) and highly significant (p-value: 0.021), even with the other factors controlled for. As was earlier demonstrated, the influence of geographic access may not be linear. Substituting the continuous measure of travel-time for quintiles (Model 6), coefficients were consistently negative but only that for quintile 5 (coef; -0.670; p-value: 0.004) was statistically significant, sensu the unadjusted univariate model (see Figure 11.8).<sup>1</sup>

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<sup>1</sup> Omitting all patients that died within a month of diagnosis (n=13) did not substantially change any of the aforementioned findings, which suggests that lower rates of referral are not being caused by death immediately following diagnosis.

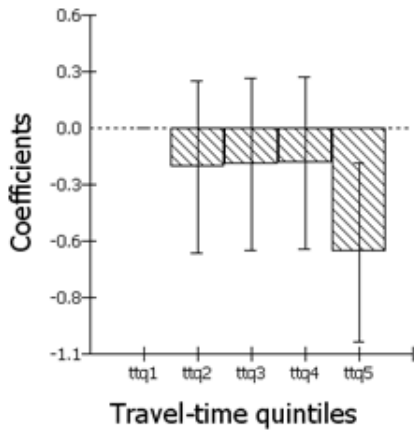
Table 11.2: Multivariate binary logit regression model: model 6 is the fully adjusted version (equation also shown)

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

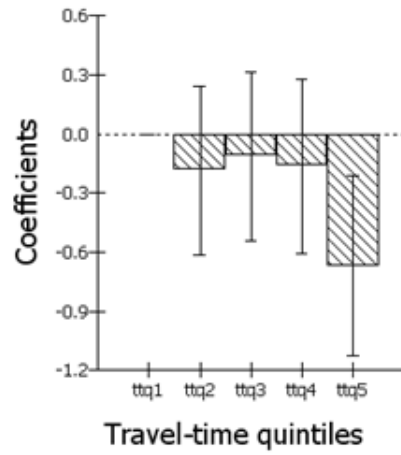
$$\text{logit}(\pi_i) = 0.871(0.344)\text{const} + -0.324(0.153)\text{Male}_i + -0.022(0.007)\text{age}_i + -0.001(0.153)\text{Yes}_i + -0.030(0.025)\text{carstair}_i + -0.187(0.218)\text{ttq}_2 + -0.114(0.217)\text{ttq}_3 + -0.165(0.225)\text{ttq}_4 + -0.670(0.234)\text{ttq}_5$$

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6													
	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value	Coefficient												
Constant	-0.214	0.126	0.090	0.515	0.246	0.037	0.512	0.296	0.084	0.535	0.305	0.079	0.990	0.364	0.007	0.871	0.344	0.011	
Sex (base: Women)																			
Men	-0.309	0.151	0.040	-0.325	0.152	0.032	-0.325	0.152	0.033	-0.322	0.152	0.034	-0.325	0.153	0.033	-0.324	0.153	0.035	
Age				-0.020	0.006	0.001	-0.020	0.006	0.002	-0.020	0.006	0.002	-0.020	0.006	0.002	-0.022	0.007	0.001	
OST (base: No)							0.003	0.151	0.982	0.011	0.152	0.944	0.012	0.153	0.935	-0.001	0.153	0.992	
Yes																			
Deprivation																			
Travel-time (log)																			
Travel-time quintiles (base: quintile 1)																			
Quintile 2																			
n (referred)	890			890			890			890			890			890			
Quintile 3																			
n (referred)	350			350			350			350			350			350			
Quintile 4																			
Pseudo R2	0.004			0.014			0.014			0.014			0.019			0.022			
Log likelihood	-594.369			-588.123			-588.123			-588.065			-585.393			-583.273			
LR chi2	4.190			16.680			16.680			16.800			22.140			26.380			
Prob > chi2	0.004			<0.001			0.001			0.002			0.001			0.001			

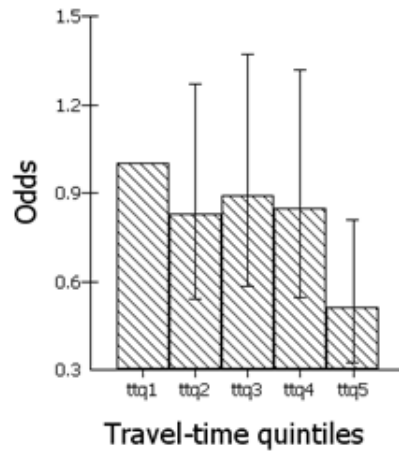
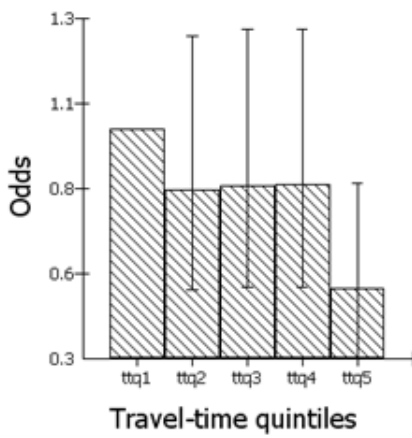
b) Univariate



b) Fully adjusted



i) Parameter with 95% confidence intervals



ii) Odds ratios with 95% confidence intervals

Figure 11.8: i) coefficients and ii) odds ratios: travel-time to HCV specialist healthcare quintiles (full-sample, (a) univariate and (b) fully-adjusted binary logit models)

## 6.7 Univariate associations (OST/non-OST stratified samples)

### 6.7.1 Introduction

Following on from the previous analyses of the full study sample, the aim of this section is to explore for potential variation between individuals with and without a history of OST, the findings of which could support or refute hypotheses as to why patients are going unreferred. The previous notation continues to apply.

### 6.7.2 Sex

#### OST

$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$   
 $\text{logit}(\pi_i) = -0.049(0.180)\text{const} + -0.396(0.216)\text{Male}_i$

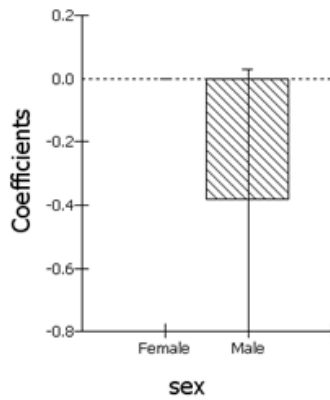
#### Non- OST

$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$   
 $\text{logit}(\pi_i) = -0.374(0.178)\text{const} + -0.220(0.211)\text{Male}_i$

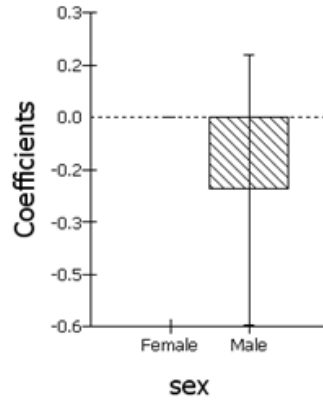
In contrast to the full sample, univariate analyses of sex to the likelihood of referral and stratified by history of OST bore no statistically significant associations, though the direction of effect was the same as previously observed.



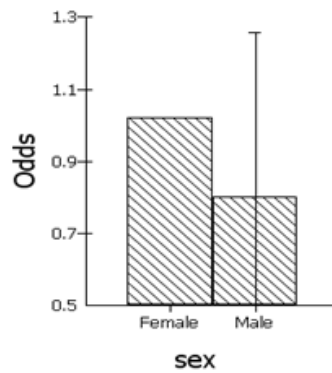
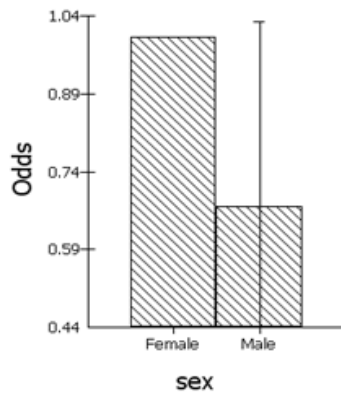
OST



Non- OST



i) Parameter with 95% confidence intervals



ii) Odds ratios with 95% confidence intervals

Figure 11.9: Univariate model i) coefficients and ii) incidence rate ratios: sex (OST and non-OST-sample)

### 6.7.3 Age

OST

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -0.486(0.507)\text{const} + 0.005(0.016)\text{age}_i$$

Non- OST

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = 0.441(0.296)\text{const} + -0.024(0.007)\text{age}_i$$

In the full sample, even after adjusting for all covariates, individuals diagnosed at an older age were significantly less likely to be referred to a specialist. The univariate models here suggest that, whilst both are again positive, the relatively large standard

error (0.016) for the OST sample renders that coefficient statistically insignificant (p-value: 0.748). Thus, older age at diagnosis only appears to be a significant influence on the likelihood of detection for patients without a history of OST (coef: -0.024; p-value: 0.001).

### 6.7.4 Deprivation

#### OST

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -0.223(0.143)\text{const} + -0.034(0.034)\text{carstair2}_i$$

#### Non- OST

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -0.579(0.109)\text{const} + 0.027(0.030)\text{carstair2}_i$$

The models for socioeconomic deprivation as the sole explanatory variable bore only weak magnitude association with the likelihood of referral for the OST (coef: -0.034) and non-OST (coef: 0.027) samples, neither of which were statistically significant to the 0.05 level.

### 6.7.5 Travel-time to specialist

#### OST

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -0.120(0.248)\text{const} + -0.083(0.091)\text{loghcvtt}_i$$

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -0.236(0.199)\text{const} + -0.201(0.305)\text{ttq2}_i + 0.045(0.296)\text{ttq3}_i + 0.110(0.301)\text{ttq4}_i + -0.477(0.315)\text{ttq5}_i$$

#### Non- OST

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

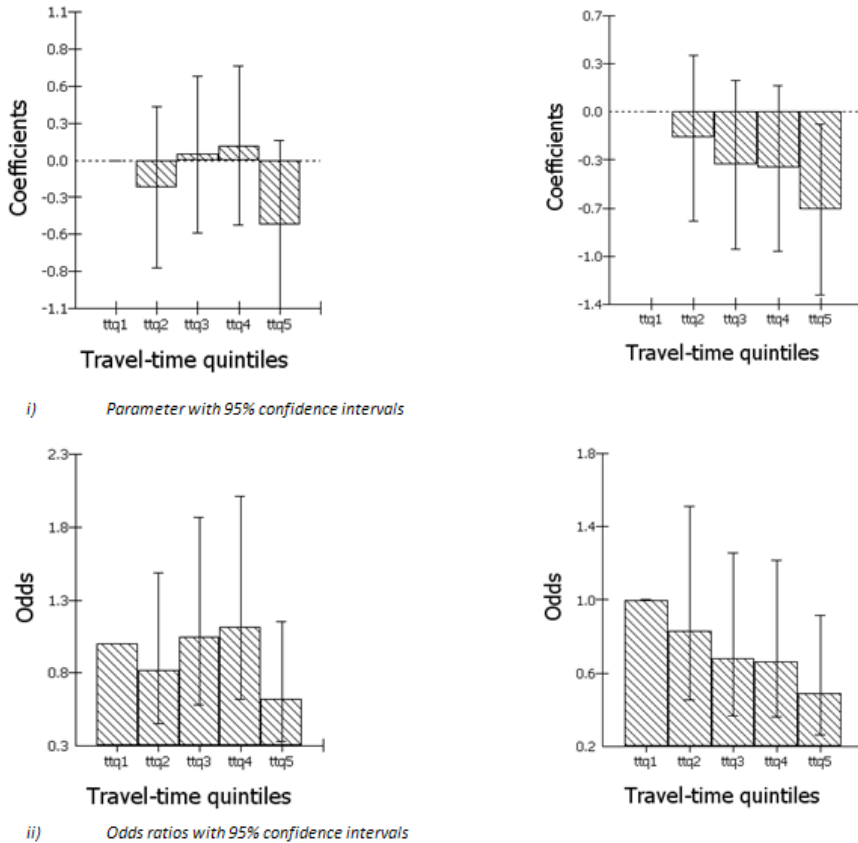
$$\text{logit}(\pi_i) = -0.017(0.256)\text{const} + -0.196(0.092)\text{loghcvtt}_i$$

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -0.182(0.229)\text{const} + -0.189(0.308)\text{ttq2}_i + -0.386(0.314)\text{ttq3}_i + -0.409(0.309)\text{ttq4}_i + -0.713(0.318)\text{ttq5}_i$$

For the measure of travel-time, the main focus of attention, interesting contrasts of association were found in univariate modelling. Whereas for the full sample, individuals

with the furthest to travel were less likely to be referred, no such association is found with statistical significance for the OST sample (coef: -0.083; p-value: 0.364) when travel-time is expressed continuously. The non-OST sample does, however, show a significantly negative association (coef: -0.196; p-value: 0.032). These results are reassuring with respect to the descriptive statistics assessed earlier.



**Figure 11.10: Univariate model i) coefficients and ii) incidence rate ratios: travel-time to specialist (OST and non-OST-sample)**

When travel-time was formatted as quintiles in testing for non-linear association, much more of the same is present with no quintile coefficient statistically significant for the OST sample (and only quintiles 2 and 5 in the direction expected). In contrast, each quintile is associated with a diminishing likelihood of referral amongst individuals without a history of OST, though only significantly so in quintile 5 (coef: -0.713; p-value: 0.025).

## 6.8 Multivariate associations (OST-sample)

Interesting contrasts have been found in univariate models between those individuals with and without a history of OST. Multivariate modelling is now required to examine the consistency of those findings, now discussed in reference to Table 11.3. Model 7 shows the preliminary model with only the statistically insignificant categorical variable pertaining to sex (coef: -0.396; p-value: 0.067). Adding age to the model (8) slightly increases the magnitude of the men/women differential (coef: -0.406; p-value: 0.062) but not to any significant degree. As was found in the univariate model, age is not a significant predictor of referral (Model 9, coef: 0.008; p-value: 0.626), nor is travel-time when expressed as a continuous variable in Model 10 (coef: -0.126; p-value: 0.189).

However, unexpectedly, the substitution of the continuous measure of travel-time for quintiles bore a marginally statistically significant association with quintile 5 (coef: -0.660; p-value: 0.048). In particular the magnitude of this quintile was quite strong and does seem to suggest that individuals with a history of OST living far from a specialist centre may be less likely to be referred than those with more favourable geographic access. The effect of adjustment for covariates on travel-time quintiles is clearer in Figure 11.11, where in univariate models the 95% confidence intervals consistently overlapped baseline. After adjustment, however, the intervals for quintile appeared to be more constrained, within the 0.05 significance level.

Table 11.3: Multivariate binary logit regression model (OST-sample): model 11 is the fully adjusted version (equation also shown)

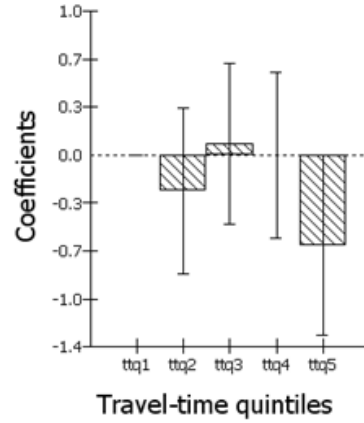
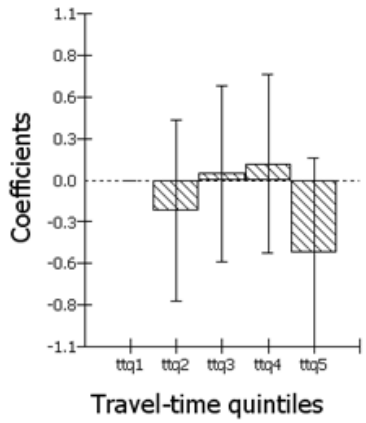
$$\text{referred}_i \sim \text{Binomial}(\text{const}_i, \pi_i)$$

$$\text{logit}(\pi_i) = 0.143(0.571)\text{const} + -0.441(0.221)\text{Male}_i + 0.005(0.017)\text{age}_i + -0.053(0.037)\text{carstair}_2 + -0.263(0.308)\text{ttq}_2 + 0.081(0.299)\text{ttq}_3 + -0.001(0.310)\text{ttq}_4 + -0.660(0.333)\text{ttq}_5$$

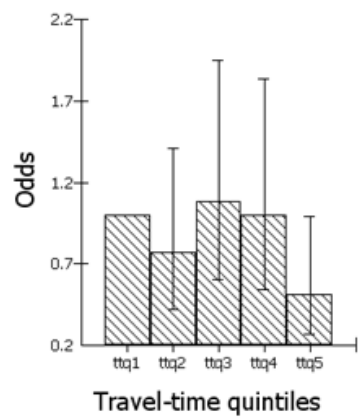
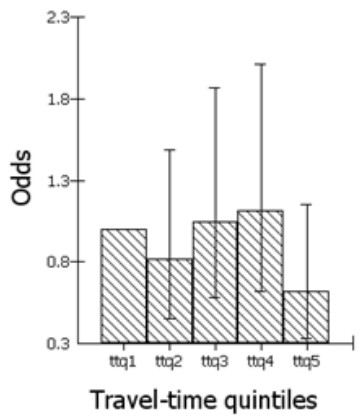
	Model 7		Model 8		Model 9		Model 10		Model 11						
	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value	Coefficient					
Constant	-0.049	0.180	0.787	-0.286	0.520	0.582	-0.225	0.525	0.668	0.141	0.595	0.812	0.143	0.571	0.802
Sex (base: Women)															
Men	-0.396	0.216	0.067	-0.406	0.217	0.062	-0.391	0.218	0.073	-0.404	0.219	0.065	-0.441	0.221	0.046
Age				0.008	0.016	0.626	0.009	0.016	0.599	0.008	0.016	0.605	0.005	0.017	0.769
Deprivation							-0.030	0.034	0.380	-0.043	0.036	0.228	-0.053	0.037	0.151
Travel-time (log)										-0.126	0.096	0.189			
Travel-time quintiles (base: quintile 1)															
Quintile 2		420											-0.263	0.308	0.394
Quintile 3		176											0.081	0.299	0.786
Quintile 4		0.006											-0.001	0.310	0.998
Quintile 5		-283.915											-0.660	0.333	0.048
N (patients)	420												420		
n (referred)	176												176		
Pseudo R2	0.006												0.011		
Log likelihood	-283.915												-282.544		
LR chi2	3.360												6.100		
Prob > chi2	0.067												0.192		

a) Univariate

b) Fully adjusted



i) Parameter with 95% confidence intervals



ii) Odds ratios with 95% confidence intervals

Figure 11.11: i) coefficients and ii) odds ratios: travel-time to HCV specialist healthcare quintiles (OST-sample, (a) univariate and (b) fully-adjusted binary logit models)

## 6.9 Multivariate associations (non-OST-sample)

To an extent, travel-time was eventually found to be significantly associated with the likelihood of referral for patients with a history of OST, once all other covariates available within the data were controlled (most of which were statistically insignificant). Whilst none of the explanatory variables were statistically significant in univariate analyses of the OST sample, age and travel-time were significantly associated with the likelihood of referral in the more heterogeneous non-OST group. Multivariate analysis is now required to assess whether age and travel-time remain significant predictors of referral after adjustment of the other covariates.

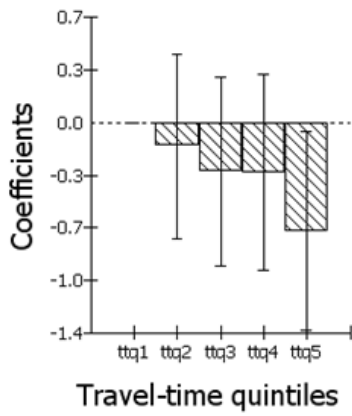
The results are illustrated in Table 11.4, with explanatory variables added sequentially. Model 12 shows the previously insignificant univariate sex differential (coef: -0.220; p-value: 0.299). Model 13 shows the result of adding in the age variable, which is negatively associated with referral (coef: -0.025) and highly significant (p-value: <0.001). Thus, after adjustment for any effect of sex, patients diagnosed at an older age are significantly less likely to be referred. Furthermore, the addition of age had the effect to strengthen the sex differential, with men even less likely to be referred (coef: -0.292), though no substantial shift in the significance level. Including the measure of socioeconomic deprivation into the model (14) yields no significant association with the likelihood of referral (coef: 0.004; p-value: 0.902), akin to the univariate model result, and does not appear to effect the other coefficients.

For the main explanatory variable, travel-time, when included in the model (15) the coefficient (-0.192) is found to be very similar to that of the univariate model (unadjusted coef: -0.196; p-value: 0.032). Now it is, however, marginally statistically insignificant at the 0.05 level (p-value: 0.053). The effect on other covariates is mixed, with what appears to be no change in the age coefficient or p-value, but a weakening of the sex differential and altering the direction of the deprivation association (though both the latter continue to be highly insignificant). All of which suggest that if travel-time to a specialist HCV centre were linearly associated with the likelihood of referral, older age at detection is the most significant explanatory variable for the non-OST sample, although the magnitude of the travel-time coefficient is relatively larger.

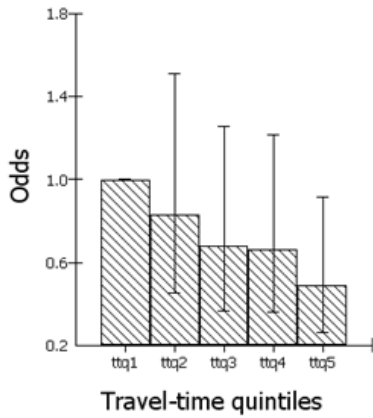
However, the previous univariate and multivariate modelling of travel-time with referral has shown that the association is more likely to be non-linear, that is, individuals living further away are several times less likely to be referred compared to those with more favourable geographic access. Model 16 substitutes the continuous measure of travel-time for the quintiles with which to explore for such non-linearity of association. In fact, a reasonably consistent negative gradient is found (Figure 11.12), with each subsequent quintile coefficient stronger than the previous. The overlapping 95% confidence intervals indicate that there is no dose-response association in this instance. In particular, the magnitude of the coefficient for quintile 5 (-0.722) is twice that of quintile 4 (-0.333), though it is also the only quintile that is significantly different to quintile 1 (p-value: 0.032).



a) Univariate



i) *Parameter with 95% confidence intervals*



ii) *Odds ratios with 95% confidence intervals*

b) Fully adjusted

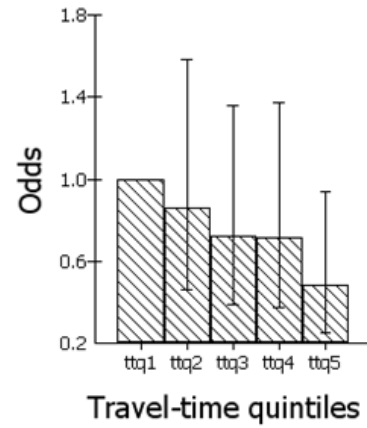
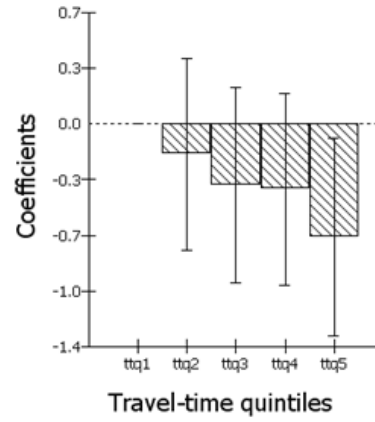


Figure 11.12: i) coefficients and ii) odds ratios: travel-time to HCV specialist healthcare quintiles (non-OST-sample, (a) univariate and (b) fully-adjusted binary logit models)

Table 11.4: Multivariate binary logit regression model (non-OST-sample): model 16 is the fully adjusted version (equation also shown)

$$\text{referred}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = 1.036(0.431)\text{const} + -0.263(0.218)\text{Male}_i + -0.026(0.007)\text{age}_i + -0.019(0.035)\text{carstar}_2 + -0.154(0.313)\text{ttq}_2 + -0.324(0.319)\text{ttq}_3 + -0.333(0.331)\text{ttq}_4 + -0.722(0.337)\text{ttq}_5$$

	Model 12		Model 13		Model 14		Model 15		Model 16						
	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value	Coefficient					
Constant	-0.374	0.178	0.036	0.684	0.347	0.049	0.670	0.366	0.067	1.213	0.463	0.009	1.036	0.431	0.016
Sex ( <i>base: Women</i> )															
Men	-0.220	0.211	0.299	-0.292	0.216	0.176	-0.292	0.216	0.176	-0.280	0.217	0.197	-0.263	0.218	0.227
Age				-0.025	0.007	<0.001	-0.025	0.007	0.001	-0.025	0.007	0.001	-0.026	0.007	0.001
Deprivation				0.004	0.031	0.902	0.004	0.031	0.902	-0.020	0.034	0.559	-0.019	0.035	0.580
Travel-time ( <i>log</i> )							-0.192	0.099	0.053						
Travel-time quintiles ( <i>base: quintile 1</i> )															
Quintile 2													-0.154	0.313	0.622
Quintile 3													-0.324	0.319	0.309
Quintile 4													-0.333	0.331	0.314
Quintile 5													-0.722	0.337	0.032
N (patients)	470			470			470			470			470		
n (referred)	174			174			174			174			174		
Pseudo R2	0.002			0.023			0.023			0.029			0.032		
Log likelihood	-309.225			-302.565			-302.558			-300.665			-299.894		
LR chi2	1.070			14.390			14.410			18.190			19.740		
Prob > chi2	0.300			0.001			0.002			0.001			0.006		

## 6.10 Discussion

In 2004, Scotland's Health Minister stated that the hepatitis C virus (HCV) "is one of the most serious and significant public health risks of our generation"(Hutchinson et al. 2006). A largely symptomless virus for many years after infection, HCV is estimated to affect more than 130 million people globally and can lead to liver cirrhosis, hepatocellular carcinoma and end-stage liver failure (Alberti, Chemello, and Benvegno 1999; Alter 2007; Shepard, Finelli, and Alter 2005). Those patients that are referred to a specialist centre later, or not at all, are more vulnerable to complications caused by the late stages of HCV infection that include hepatocellular carcinoma (HCC) and cirrhosis (Giacosa and Hill 1996; Ince and Wands 1999; Perz and Alter 2006; Perz et al. 2006). Treatment is more difficult for patients in later stages of infection, with palliative care or a liver transplant sometimes the only options. The limited access, high cost and inconsistent outcomes of liver transplantations (Prasad and Lodge 2001; Rocca, Yawn, Wollan, and Kim 2004) only further emphasise the importance of referring patients for specialist consultation whilst there is still a favourable window of opportunity for intervention.

This study contributes further evidence to the increasing number of reports that fewer than half of patients diagnosed with HCV are referred to an HCV specialist centre (Pareek, Wiselka, and Grant 2007; The Hepatitis C Trust and The University of Southampton 2005; The Scottish Government 2008). Previous studies have suggested

that GP referral decisions are influenced by a range of factors that broadly fit into four categories: i) GP associated factors (e.g. knowledge, personality, relationships with patients, colleagues and consultants); ii) patient associated-factors (e.g. socioeconomic characteristics, expectations, beliefs); iii) case-specific factors (e.g. type of condition, perceived seriousness); and iv) structural factors (e.g. waiting lists, geographic access to specialists)(O'Donnell 2000). This study has demonstrated that patients with the furthest to travel seem less likely to be referred to an HCV specialist centre.

This finding fits with other studies of referral for cardiac rehabilitation (Grace et al. 2008), renal replacement therapy (Boyle, Kudlac, and Williams 1996a), and others (Iredale, Jones, Gray, and Deaville 2005; Jones 1987; Madeley, Evans, and Muir 1990) each having demonstrated statistically significant decreasing rates of referral as distance from specialist centres increases. By way of an attempt to explain why geography seems to matter for referral to an HCV specialist centre, I explored whether patients with a history of IDU and living in more remote areas were less likely to be referred. Although the indicator of OST did not identify all those with a history of IDU, it did subdivide the study population by those that are known by the NHS to have had prior engagement because IDU-related issues. Thus, the OST variable identified a group at greater potential risk of IDU-related discrimination, which may be more likely in remote areas. Patients with a history of OST were no less likely to be referred than those without, and the observed travel-time decay association persisted for groups of patients.

This suggests the chances of referral are not lower in more remote areas because of a greater potential for IDU-related discrimination.

Men were consistently less likely to be referred than women (though, curiously only in models of the full sample, not when stratified by history of OST), and this has also been reported in Australia (Stoové, Gifford, and Dore 2005; Temple-Smith et al. 2007), where a survey also suggested that those patients more likely to be referred: i) had a longer time since diagnosis; ii) received a longer consultation time; iii) were experiencing HCV-related symptoms; iv) were not current IDU; v) were seeing a GP specifically for HCV (Stoové, Gifford, and Dore 2005). The data did not have information on the date referred so the length of time between diagnosis and referral could not be calculated if some patients were delayed because of alternative healthcare arrangements. I did not have information on the length of consultation time, but whereas some research has found that consultation times in general are shorter for patients in more deprived areas,(Mercer and Watt 2007) we found no significant association at all between referral and deprivation. It may be that GPs serving deprived areas are more familiar with HCV referral protocol through harm-reduction strategies, balancing any potential effect of shorter consultation times. There was no information available as to why people visited their GP and so could not investigate whether those consulting specifically for HCV infection were more likely to be referred.

The ecological fallacy is an issue because of the use area-based measures of deprivation and travel-time, though the use of Output Areas represents the best possible attempt to control out these effects whilst maintaining the anonymity of the patients. Individual-level data on socioeconomic position could lead to different associations related to disadvantage. Further developments in GIS tools and data resources on public transport availability, frequency and expense may provide a more rounded picture of geographic access to healthcare in future studies. Finally, the absence of detailed and reliable HCV data from other NHS boards restricted the study population to NHS Tayside, but the emergence of such data on a national scale would be useful for more sophisticated follow up research if available.

## **6.11 Summary**

### **6.11.1 What we knew before?**

Rates of referral of patients infected with hepatitis C (HCV) to specialist centres in the UK are low. Knowledge of HCV varies amongst general practitioners (GPs) and there have been reports of discrimination related to intravenous drug use (IDU). It is possible that awareness may be poorer amongst GPs in more remote areas, which could lead to lower chances of referral for patients, but no study has explored this possibility so far.

### **6.11.2 What this study has contributed?**

Patients living furthest from an HCV specialist centre suffered lower odds of referral. It seems probable that patients in more remote areas suffer lower odds of referral because of less awareness of HCV amongst GPs, rather than due to IDU-related discrimination as the travel-time decay was reported for patients with and without a history of IDU known to the NHS. Raising awareness of HCV and HCV referral protocol amongst GPs that have less frequent contact with individuals that have a history of IDU, or HCV infection, may increase rates of referral to specialist centres.

### **6.11.3 What gaps remain?**

This study demonstrated that a lack of geographic access to specialist HCV healthcare is associated with poorer odds of referral. Several questions remain, however, such as what becomes of those patients that are not referred? And despite a GP introducing their patients by means of referral to a HCV specialist centre, are patients lacking geographic access likely to attend their appointment? What effect will the selective processes of detection and referral have for HCV-related outcomes and will geographic accessibility be influential in the clinical pathway from diagnosis to the successful clearance of the virus?

# **7. Are patients with further to travel less likely to utilise HCV specialist centres?**

## **7.1 Introduction**

In Scotland, the majority of persons chronically infected with Hepatitis C (HCV) remain undiagnosed and many of those diagnosed fail to reach and stay within HCV specialist care services (Parkes, Roderick, Bennett-Lloyd, and Rosenberg 2006; The Scottish Government 2008). According to the Hepatitis C Action Plan for Scotland (The Scottish Government 2008) nearly 50% of newly diagnosed individuals, referred to HCV specialist centres, do not attend their appointment. Referral to an HCV specialist centre gives patients the opportunity to consult medical staff on appropriate courses of treatment, can offer a differential diagnosis, expert clinical management, an assessment of the stage of infection and advice on precautionary measures to avoid secondary infection (Brown 2002; Scottish Intercollegiate Guidelines Network 2006).



The previous chapter demonstrated findings which suggested that individuals diagnosed with HCV residing long travel-times away from an HCV specialist centre are less likely to be referred in comparison to those with more favourable geographic accessibility. In this chapter, attention turns to the question of what happens to a patient after the GP makes the referral to an HCV specialist centre? So what if an appointment is scheduled for the patient to visit the specialist centre; do they elect to attend? And if they do decide to travel all the way to their first appointment, does this mean that they will continue to utilise the specialist HCV healthcare until discharged by medical staff? If not, to what extent could a lack of geographic access help to explain the current underutilisation of HCV specialist centres in Scotland?

The lack of utilisation of HCV specialist centres is a policy concern (Parkes, Roderick, Bennett-Lloyd, and Rosenberg 2006; The Hepatitis C Trust and The University of Southampton 2005; The Scottish Government 2008). In order to improve rates of utilisation, policy makers need knowledge of what is causing the low uptake of referral, and for those patients that do attend their initial appointment, studies need to explore which factors are influencing continued utilisation? As was emphasised earlier, awareness amongst the public of HCV infection, even those positively diagnosed, is quite low and the same goes with regard to HCV treatment. Unless a patient has a knowledgeable GP, able to convey the significance of attending the referral appointment and the importance of keeping up with the follow-up visits, patients may be less likely to utilise the specialist HCV healthcare. However, the previous chapter

found that those patients living furthest from an HCV specialist centre were less likely to be referred, with the probable explanation being a lower level of awareness amongst GPs situated in more remote, rural communities. Hence, patient utilisation of the specialist centres may follow a similar spatial pattern.

For those patients lacking geographic access to attend their first appointment, after which awareness would be expected to be less of an issue, could geography cease to be important? Maybe, but this would depend upon how affordable and acceptable it is for the patient to keep travelling frequently to the specialist centre, possibly in receipt of treatment that often has quite debilitating side-effects. Even to the most affluent of patient, sustaining frequent visits to hospital over a long period of time may be more difficult amongst those living quite far away, especially amongst individuals with limited transport options (e.g. the elderly) (Bentham and Haynes 1985; Joseph and Bantock 1982; Nemet and Bailey 2000).

No study has explored whether a lack of geographic access is associated with a lower likelihood of utilisation of HCV specialist centres. This aim of this chapter is to make a start filling this gap in the literature, finding evidence to answer the following research questions:

1. To what extent are individuals with poorer geographic access to an HCV specialist centre less likely to attend their first referral appointment?

2. Amongst those that do attend their first appointment, to what extent is a lack of geographic access to an HCV specialist centre associated with the increased likelihood of patient-loss of follow-up?

## **7.2 Methodological approach**

In this chapter, like the previous chapter that explored whether geographic access influenced patient referral, the response variables for the forthcoming analyses are also dichotomous. More specifically, there are two response variables: with the first pertaining to whether a patient did or did not attend their first appointment; and the second indicative of long-term loss of follow-up. Thus, a logistic regression model is also appropriate, with positive coefficients and odds ratios above 1 indicating the increased likelihood of the fitted response occurring, whereas negative coefficients and odds ratios below 1 suggest a decreased likelihood (see chapter 6 for further detail).

## **7.3 Study specification**

### **7.3.1 Study sample and setting**

This study was made possible through the use patient records extracted from Tayside HCV Clinical Database. This is a routinely-collected, fully anonymised database which included patients that had been referred to the specialist centre (Ninewells Hospital). Information for each patient was available on the attendance of the first appointment and long-term follow-up. All patients had full age, sex, and 2001 Output Area of residence information, were at least 15 years old and were not in prison. Essentially, the sample comprised the referred patients from the analyses of the previous chapter. However, the sample here is larger because of the temporal overlap, as access to data within the ELDIT was only available up to 2003, but the Clinical Database held patient records also for the years 2004-2006. Also because of just the one dataset being used, the self-reported IDU history variable can be used instead of the OST surrogate of previous chapters. Finally, as with previous analyses, the study setting was restricted to NHS Tayside, where geographic accessibility to the HCV specialist centre can vary substantially. Those patients within the Tayside HCV Clinical Database but living in Output Areas outside the healthboard boundary were omitted for the same reasons to before.

### 7.3.2 Variable definition

At this point, there are some fairly important details that need to be imparted with regards to the definition of the response variables. The Tayside HCV Clinical Database had a two-level record of HCV specialist centre utilisation for each referred patient. Those that did not attend their first appointment were coded as 'did not attend.' All other patients 'attended' at least once, after which there were four other possible status categories: i) 'continued follow-up'; ii) 'discharged'; iii) 'deceased'; and iv) 'lost to follow-up.' 'Continued follow-up' includes all patients that had attended their last scheduled appointment. 'Discharged' refers to patients that required no further consultations. 'Deceased' identifies patients that had died whilst in follow-up. 'Lost to follow-up' refers to patients that did attend their first appointment, but at some point, did not attend their last scheduled appointment. Patients in the 'continued follow-up,' 'discharged' and 'deceased' groups were aggregated together to form a group called 'adhered,' in contrast to those that were 'lost' at some point.

Therefore, the first response variable on attendance of the first appointment was coded as follows: (1) 'did not attend'; (0) 'attended'. The second response variable on long-term utilisation was coded as: (1) 'lost to follow-up'; (0) 'adhered'. Patient records contained a self-disclosed history of IDU classified into four categories: i) never injected; ii) injected within the last 12 months; iii) last injected over 12 months before detection; iv) unknown/not disclosed. Due to small numbers, we created a binary variable which

classified patient history of IDU into a dichotomous variable: 'never injected' or 'injected,' the latter aggregating patients that disclosing current or past injecting behaviour. Patients for whom this information was unknown/not disclosed were omitted from the analysis (n=32).

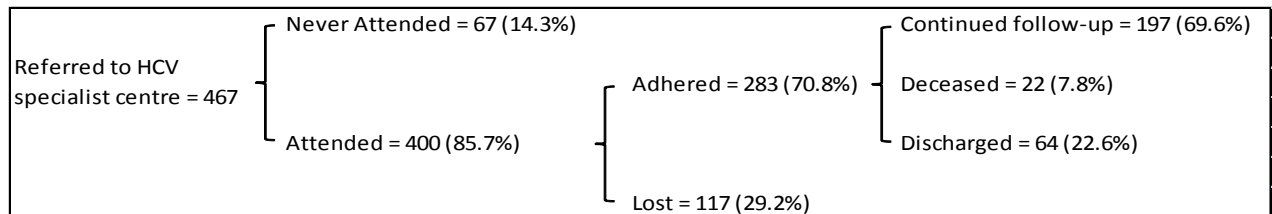
Utilisation is likely to be influenced by patient socioeconomic position (SEP), with those occupying less favourable positions having less access to transport, less flexibility of time and more likely to be suffering poor health (Galobardes, Lynch, and Davey Smith 2007). In the absence of individual-level data, the Carstairs index of deprivation score of where the patient lived (Carstairs and Morris 1989a) continued to proxy socioeconomic disadvantage. A measure of travel-time from the patient Output Area of residence to the HCV specialist centre at Ninewells Hospital was used as the main test variable. The same method in terms of using geometric centroids, average speeds and distinguishing between different types of road also applies here. Higher scores indicate longer travel-times and poorer geographic access to specialist HCV healthcare.

### **7.3.3 Analysis specification**

Binary logistic regression was used to estimate the effect of travel-time to the HCV specialist centre on: i) first appointment attendance (1='never attended,' 0='attended'); and ii) long-term follow-up (1='lost,' 0='adhered'). For modelling purposes, the travel-time measure was calculated as a natural logarithm to reduce problems of skewness.

Travel-time quintiles were also used to explore for non-linear effects. Interactions were calculated for age and travel-time, to account for the possibility that older people in more remote areas may find utilisation more difficult.

## 7.4 Descriptives



**Table 12.1: Definition of referral attendance and adherence status**

Table 12.1 summarises the sample size by the utilisation typology outlined above. Of the 467 patients diagnosed and referred to the HCV specialist centre at Ninewells Hospital, 400 attended their first appointment at the specialist centre (85.7%) whereas 67 did not attend (14.3%). At first glance, these percentages appear far more favourable than the 50% reported previously in the Action Plan (The Scottish Government 2008). Of those that attended the first appointment, 283 (70.8%) patients had adhered to follow-up appointments, comprising 197 (69.6%) in continued follow-up and 64 (22.6%) that were discharged following completion. 22 (7.8%) patients were known to have deceased. In contrast, 117 (29.2%) were subsequently lost to follow-up at some point after their first appointment.

Table 12.2 describes some of the characteristics of the study population. For each response variable, 62.7% to 69.2% of patients were men, to the 30.8%-37.3% for women. Patients that never attended the specialist centre tended to be younger on average (28.1 years) than those that did (35.2 years). Similarly, patients that continued to adhere to the follow-up appointments were older on average (36.1 years) compared to those that were lost to follow-up (33.1). High percentages of patients in each response variable had a history of IDU, though these rates were highest amongst those that did not attend the first appointment (97.0%) and those that were subsequently lost to follow-up (80.3%). Similarly, whilst the mean socioeconomic deprivation of each group was relatively high, higher scores were observable for patients that never attended (3.1) and those that were lost to follow-up (3.1).

Characteristic	First appointment		Long-term follow-up status	
	Attended	Never attended	Known	Lost
Number of males (%)	275 (68.8)	42 (62.7)	194 (68.6)	123 (69.2)
Number of females (%)	125 (31.2)	25 (37.3)	89 (31.4)	61 (30.8)
Mean age (years)	35.2	28.1	36.1	33.1
Number of current or former IDU (%)	278 (69.5)	65 (97.0)	184 (65.0)	94 (80.3)
Mean socioeconomic deprivation	2.3	3.1	2.0	3.1
Mean centre travel (mins)	21.1	21.5	21.9	19.0
Number of patients (%)	400 (85.7)	67 (14.3)	283 (70.8)	117 (29.3)

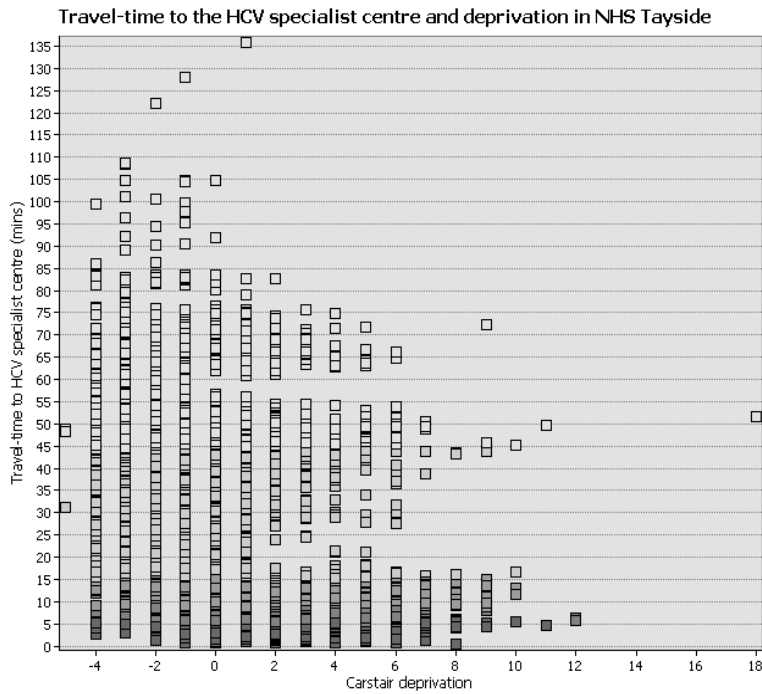
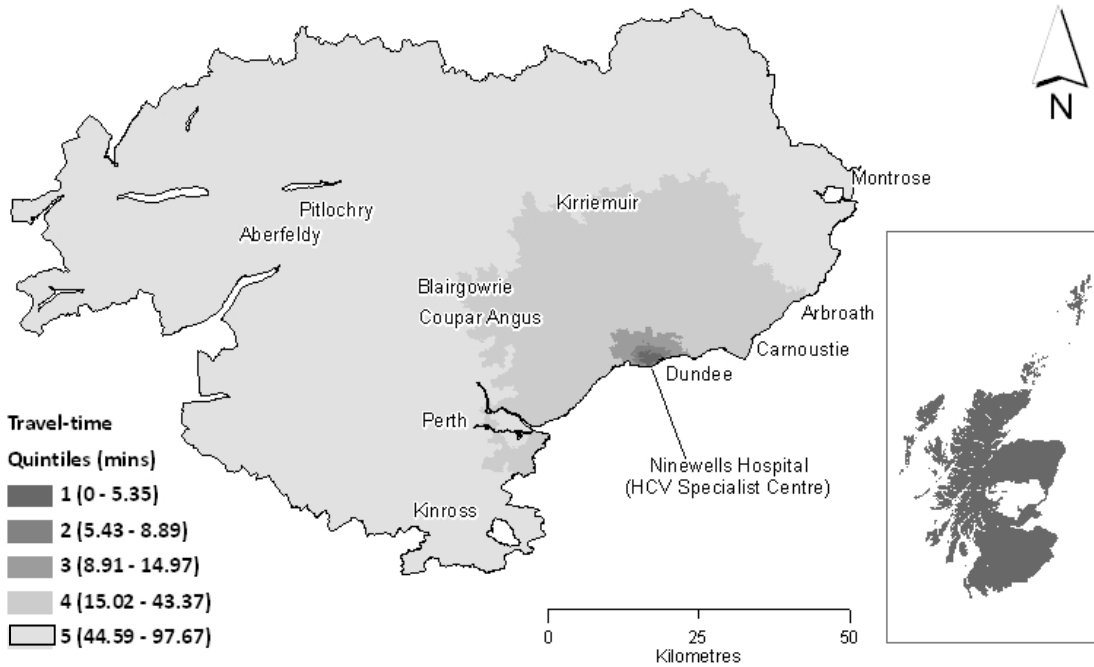
**Table 12.2: Referred population descriptive characteristics**

The mean travel-time from patient residence to the specialist centre was very similar for both those patients that attended their first appointment (21.1 minutes) and those that did not (21.5 minutes). Mean travel-times were marginally longer for those patients that adhered to the follow-up appointments (21.9 minutes) compared to those that were lost mid-follow-up (19.0 minutes). The geographical extent of travel-time to the HCV specialist centre in Tayside is illustrated in Figure 12.1, which also displays a



harmonised scatterplot showing that Output Areas with less geographic access tended to be less socioeconomically deprived.

**Figure 12.1: Study setting: travel-time to the HCV specialist centre and socioeconomic deprivation (map and scatterplot)**



Figures 12.2 - 12.4 illustrates percentages of the first-appointment utilisation response variable stratified by travel-time quintiles. Small percentages for patient non-attendance were evident across all travel-time quintiles and did not vary substantially

(Figure 12.2). Nor did there appear to be any gradient when considering sex or history of IDU (Figure 12.3 and 12.4 respectively). Notably, the percentages of women not utilising their first appointment was twice those observed for men in quintiles 4 and 5, whilst the percentage non-attendance for men was only larger (marginally) than for women in quintile 2. All patients without a history of IDU in quintiles 3-5 utilised their first appointment, whereas only very small percentages in quintiles 1 and 2 did not attend.

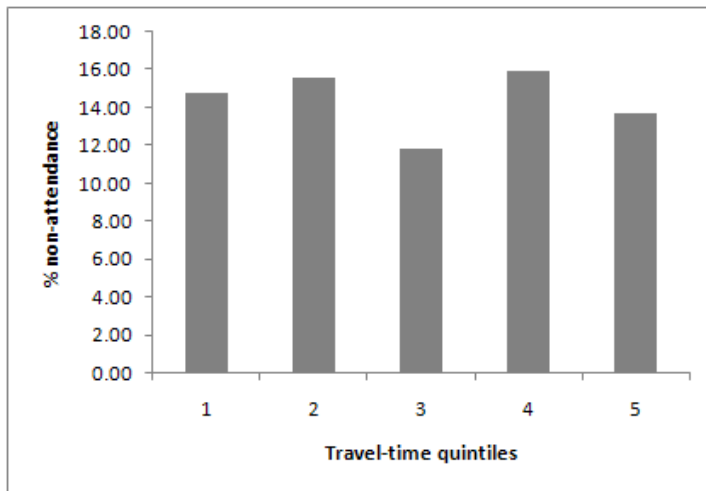


Figure 12.2: Percentage non-attendance of the first appointment at an HCV specialist centre, by travel-time

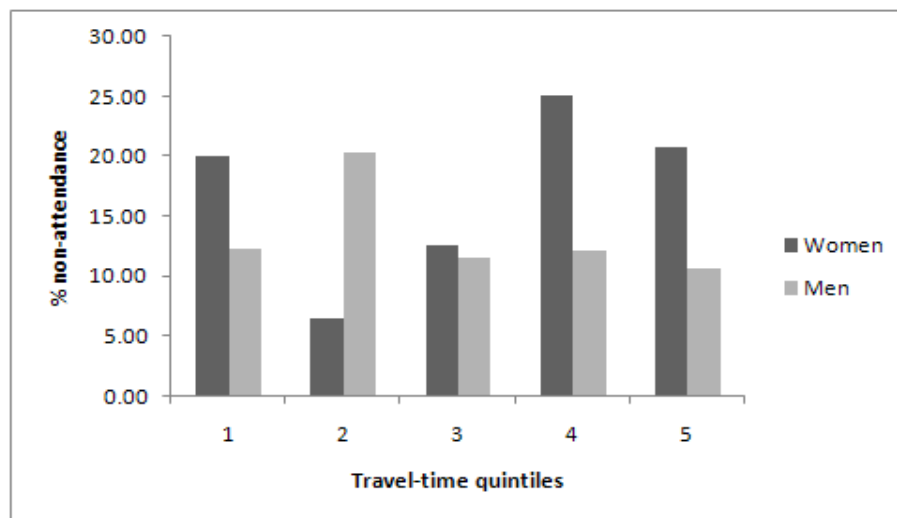


Figure 12.3: Percentage non-attendance of the first appointment at an HCV specialist centre, by sex and travel-time

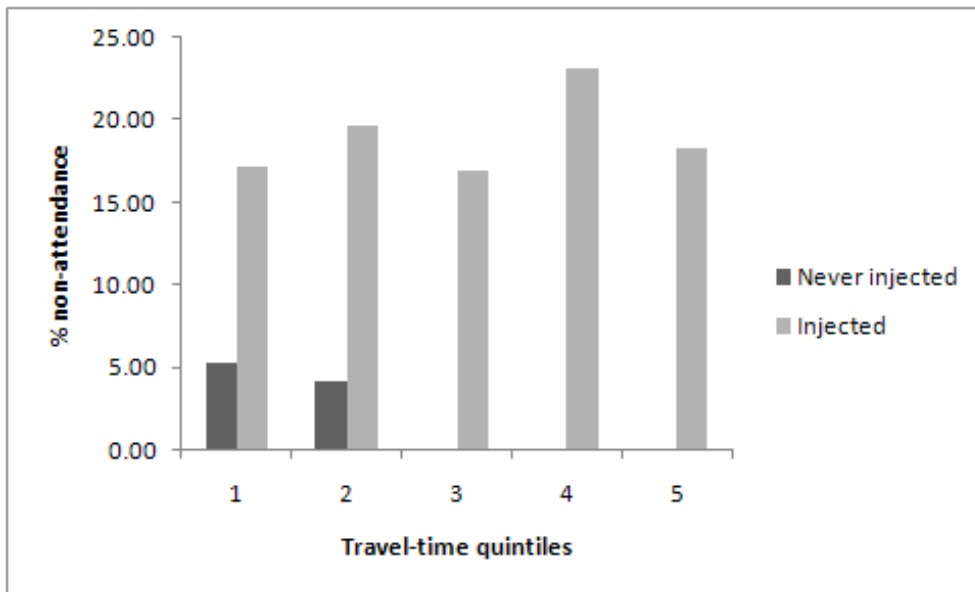


Figure 12.4: Percentage non-attendance of the first appointment at an HCV specialist centre, by history of IDU and travel-time

In the case of long-term patient follow-up, Figures 12.5 - 12.7 illustrate percentages of the response variable stratified by travel-time quintiles and covariates. Percentages of patients lost to follow-up appeared to vary across travel-time quintiles, resembling a reasonably smooth gradient counterintuitive to what was expected (Figure 12.5), with lower rates of lost patients in quintiles 4 and 5 (those with the furthest to travel to a specialist).

Trends were less consistent when grouping by sex (Figure 12.6) and history of IDU (Figure 12.7). The percent loss of follow-up for women tended to fluctuate substantially between quintiles, though the aforementioned counterintuitive gradient appeared for men (Figure 12.6). Similarly, the percentage loss of follow-up of patients with no history of IDU was notably lower amongst those living further from the specialist centre, whilst no consistent trend was clear amongst those with an IDU history (Figure 12.7).

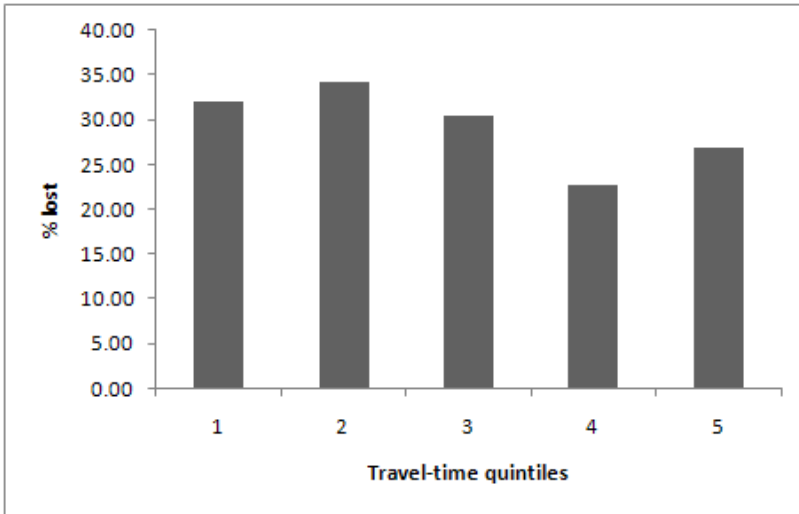


Figure 12.5: Percentage of patients lost to follow-up at an HCV specialist centre, by travel-time

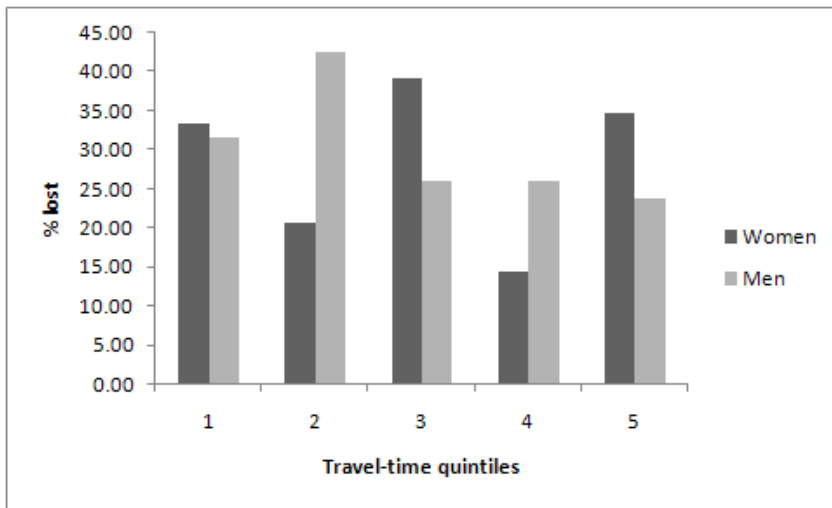


Figure 12.6: Percentage of patients lost to follow-up at an HCV specialist centre, by sex and travel-time

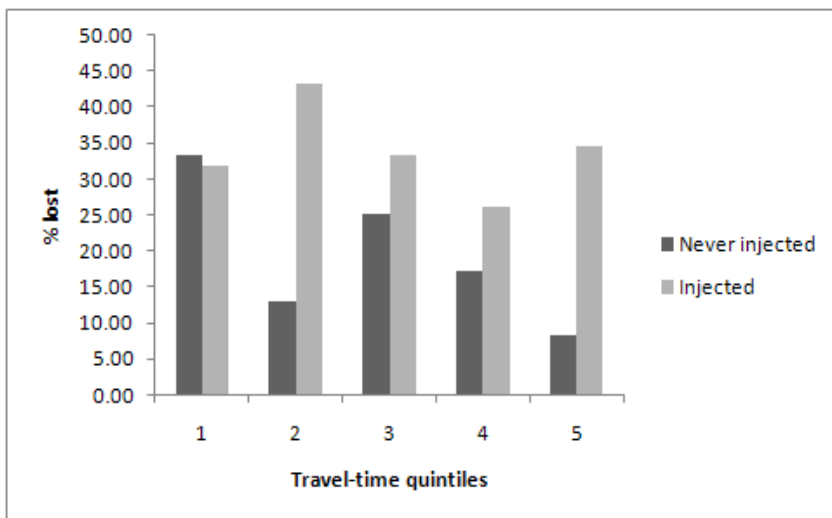


Figure 12.7: Percentage of patients lost to follow-up at an HCV specialist centre, by history of IDU and travel-time

## 7.5 Univariate associations (non-attendance)

### 7.5.1 Introduction

As has been the procedure in previous chapters, univariate regression models are employed to test association between response and individual explanatory variables. This aids interpretation of the extent to which other covariates adjust the univariate association when put into the full model. The notation for the logistic null model is:

$$\begin{aligned} \text{non-attendance}_i &\sim \text{Binomial}(\text{cons}_i, \pi_i) \\ \text{logit}(\pi_i) &= \beta_0 \text{cons} \end{aligned}$$

where 'non-attendance' denotes the full-sample of referred patients being used as the response variable (1 = 'did not attend', 0 = 'attended') and ' $\beta_0$ ' the parameter for the model constant.

### 7.5.2 Sex

$$\begin{aligned} \text{non-attendance}_i &\sim \text{Binomial}(\text{cons}_i, \pi_i) \\ \text{logit}(\pi_i) &= -1.609(0.219)\text{cons} + -0.270(0.275)\text{Men}_i \end{aligned}$$

The first univariate logistic model tests the differential association between men and women and the likelihood of non-attendance (first appointment). Women were set at baseline with the coefficient for men allowed to vary. Non-attendance was less likely for men relative to women (coef: -0.270), though the 95% confidence intervals

overlapping baseline suggest that this association is not statistically significant (p-value: 0.326).

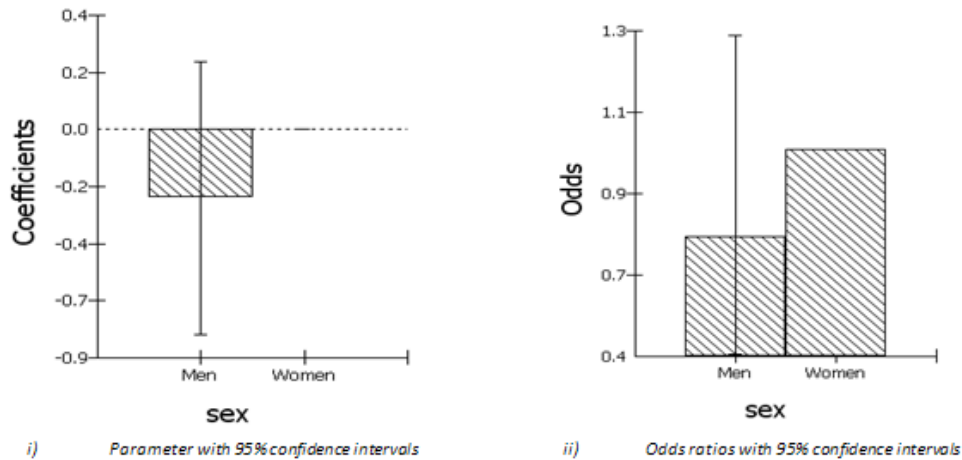


Figure 12.8: Univariate model i) coefficients and ii) incidence rate ratios: sex (non-attendance)

### 7.5.3 Age

$$\text{non-attendance}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = 1.726(0.612)\text{cons} + -0.113(0.021)\text{age}_i$$

The likelihood of non-attendance associated negatively with age (coef: -0.113), meaning that for every one year older an individual is at the time of diagnosis, the likelihood of not utilising the first appointment decreases by 0.113 in the log of the odds. Moreover, because the standard error is relatively small (0.021), this association is highly significant (p-value: <0.001).

### 7.5.4 Deprivation

$$\text{non-attendance}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -1.991(0.181)\text{cons} + 0.075(0.041)\text{carstair2}_i$$

Variation in the utilisation of specialist healthcare by socioeconomic position has been discussed in previous chapters. In this univariate model, patients experiencing higher

levels of socioeconomic deprivation were more likely not to attend (coef: 0.075). Although this association is generally expected, however, the relatively large standard error (0.041) means that it is marginally statistically insignificant (p-value: 0.068).

### 7.5.5 IDU history

non-attendance<sub>i</sub> ~ Binomial(cons<sub>i</sub>, π<sub>i</sub>)

$$\text{logit}(\pi_i) = -4.111(0.712)\text{cons} + 2.658(0.725)\text{Injected}_i$$

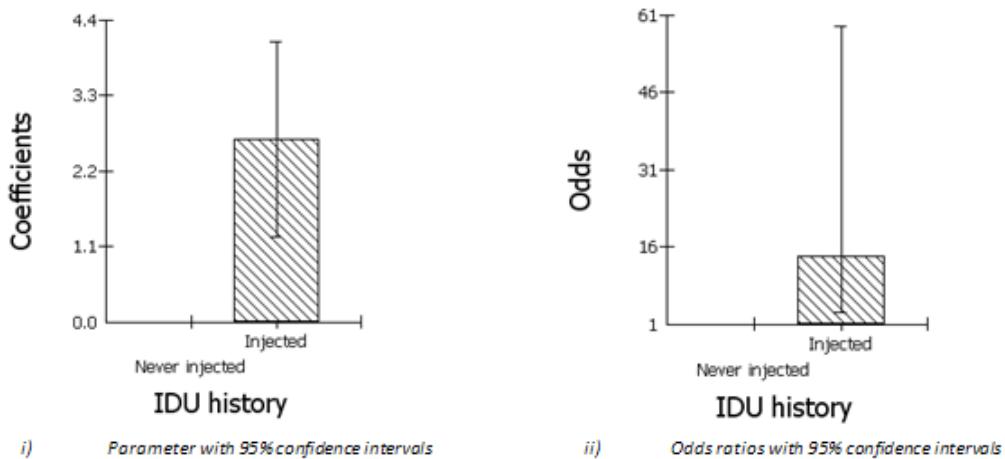


Figure 12.9: Univariate model i) coefficients and ii) incidence rate ratios: IDU history (non-attendance)

IDU history has been a central variable of focus in a number of theses, mainly in the US, that examine attendance to HCV specialist centres. The predominant finding is that patients with a history of IDU are less likely to attend and this is also the general association in this univariate logistic model (coef: 2.658). In this case, it is also helpful to interpret the association as an odds ratio, as shown in Figure 12.9, where the odds of an individual with a history of IDU not utilising their first appointment is 14.263 times higher than those without. This is a very large association and it is in some part predictable, as the earlier descriptive statistics showed 97% of patients not attending their first appointment had some history of IDU. Furthermore, although the statistical



significance is high (p-value: <0.001), the very wide 95% confidence intervals suggest uncertainty of the overall magnitude of association, which could range from 3.437 up to 59.187.

### 7.5.6 Travel-time

$$\text{non-attendance}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -1.817(0.341)\text{cons} + 0.012(0.123)\text{loghcvtt}_i$$

Any potential association between the likelihood of non-attendance and geographic access to the specialist was the primary focus of attention. In the univariate model, the coefficient was positive (0.012), which fitted with suspicions that individuals with further to travel would be less likely to utilise their referral appointment. However, the relatively large standard error meant that this association was highly insignificant (p-value: 0.922).

$$\text{non-attendance}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -1.755(0.289)\text{cons} + 0.064(0.410)\text{ttq}_2 + -0.253(0.432)\text{ttq}_3 + 0.094(0.404)\text{ttq}_4 + -0.086(0.416)\text{ttq}_5$$

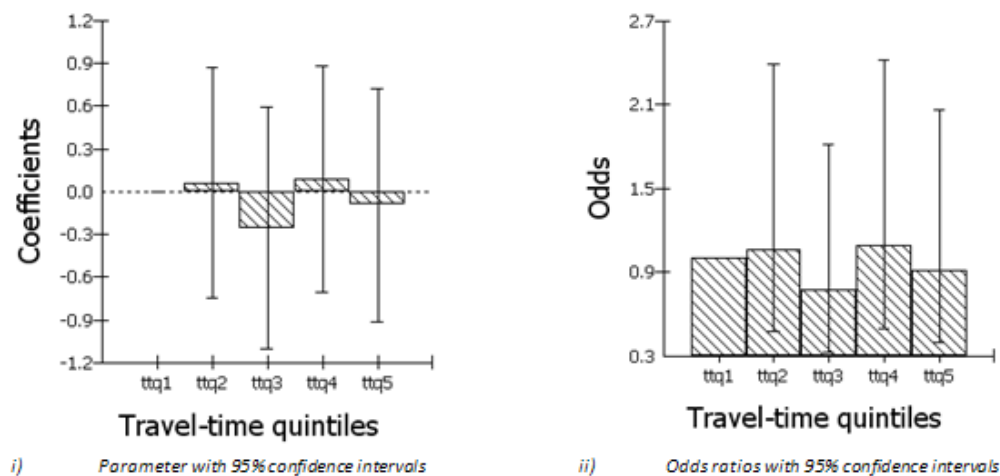


Figure 12.10: Univariate model i) coefficients and ii) incidence rate ratios: travel-time to specialist (non-attendance)

It was possible that the influence of travel-time on the likelihood of not attending the first appointment was not linear, with individuals with the furthest to travel suffering disproportionately from those with more favourable geographic accessibility. In an attempt to explore for non-linearity, quintiles were substituted into the model. Evidently from Figure 12.10, no consistent gradient of association was observed and none of the quintiles were significantly different to the baseline. Thus, in a univariate model, no statistically significant association between geographic access to the specialist centre and the likelihood of utilising the first appointment was found. However, multivariate logistic regression modelling was then pursued to explore whether associations were found after adjusting for the other covariates.

## **7.6 Multivariate associations (non-attendance)**

Table 12.11 shows the results of multivariate logistic regression model, fitting the likelihood of non-attendance as the response and each of the previously tested explanatory variables sequentially. In Model 1, the statistically insignificant differential association between men and women, familiar from the first univariate test. Model 2 sees the addition of the age variable, previously highly significant in the univariate model and similarly in this (coef: -0.112; p-value: <0.001). Socioeconomic deprivation in Model 3 is again positively associated with the likelihood of not attending the first

appointment (coef: 0.028), but unlike the marginally significant association of the univariate test, it is not at all significant in this model (p-value: 0.534). The deprivation (0.014) and age (-0.097) coefficients were also attenuated by the introduction of the IDU history categorical variable in Model 4, which continues to demonstrate the positive association as previously found (coef: 2.201; p-value: 0.003).

As was observed in the univariate test, the continuous measure of travel-time in Model 5 appeared to be positively associated with the likelihood of non-attendance (coef: 0.038), but was not significant with adjustment for the covariates (p-value: 0.777). The inconsistent and statistically insignificant trend for travel-time quintiles also found in the univariate model emerged in Model 6. Given the persistently significant age coefficient and older individuals with poorer levels of geographic access thought to be less likely to utilise specialist healthcare, an interaction between age and travel-time was fitted in Model 7. Despite all the coefficients being in the hypothesised direction, all the 95% confidence intervals were overlapping baseline so none of the coefficients were statistically significant to the 0.05 level. Thus, in this case, it seems that geographic accessibility has no influence upon utilisation of first appointments among individuals referred to an HCV specialist centre in NHS Tayside.

Table 12.3: Multivariate logit regression model: model 7 is the fully adjusted version (equation also shown)

$$\text{non-attendance}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = 0.639(1.646)\text{cons}_i + 0.290(0.300)\text{Men}_i + 0.142(0.050)\text{age}_i + 0.017(0.048)\text{carstair}_2 + 2.184(0.740)\text{injected}_d + 0.328(2.051)\text{ttq}_3 + 0.639(1.922)\text{ttq}_4 + 0.019(0.071)\text{ttq}_2 + 0.118(0.070)\text{ttq}_3 + 0.050(0.066)\text{ttq}_4 + 0.056(0.071)\text{ttq}_5 + \text{age}_i$$

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value	Coefficient
Constant	-1.609	0.219	<0.001	1.794	0.625	0.004	1.661
Sex (base: women)							
Men	-0.270	0.275	0.326	-0.148	0.289	0.609	-0.138
Age							
Age				-0.112	0.021	<0.001	-0.110
Deprivation							
Deprivation				0.028	0.045	0.534	0.014
IDU history (base: never injected)							
Injected				2.201	0.736	0.003	2.201
Travel-time to specialist centre (log)							
Travel-time to specialist centre (log)				0.038	0.133	0.777	0.038
Travel-time quintiles (base: quintile 1)							
Quintile 2							
Quintile 2				0.198	0.437	0.651	-0.328
Quintile 3				-0.013	0.456	0.978	-3.551
Quintile 4				0.329	0.445	0.460	-1.100
Quintile 5				-0.007	0.453	0.987	-1.591
Travel-time quintiles*age interaction (base: quintile 1)							
Quintile 2*age							
Quintile 2*age				0.019	0.048	0.696	0.017
Quintile 3*age							
Quintile 3*age				2.201	0.738	0.003	2.184
Quintile 4*age							
Quintile 4*age				0.056	0.071	0.432	0.056
Quintile 5*age							
Quintile 5*age				0.019	0.071	0.795	0.019
N (referred patients)	467			467			467
n (not-attended)	67			67			67
Pseudo R2	0.003			0.149			0.159
Log likelihood	-191.562			-163.465			-161.416
LR chi2	0.950			57.140			61.240
Prob > chi2	0.330			<0.001			<0.001

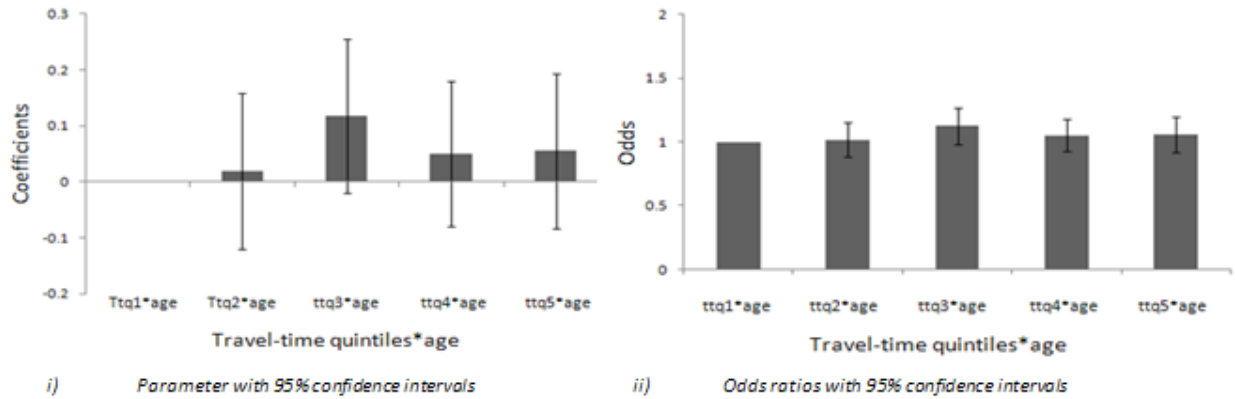


Figure 12.11: Multivariate model i) coefficients and ii) incidence rate ratios: travel-time to specialist\*age (non-attendance)

## 7.7 Univariate associations (lost to follow-up)

### 7.7.1 Introduction

Moving to the second research question of this chapter, on measuring the extent to which geographic access might influence the continued utilisation of an HCV specialist centre amongst those individuals that have attended at least once. Once again, logistic regression method was used but with the dichotomous response variable changing to: (1) 'lost' (to follow-up); (0) 'adhered' and with very similar notation:

$$\text{lost}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = \beta_0 \text{cons}_i$$

where 'lost' denotes the sub-sample of referred patients that had attended the HCV specialist centre at least once (n=400) and 'βo' the parameter for the model constant.

### 7.7.2 Sex

$$\text{lost}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -0.905(0.198)\text{cons} + 0.032(0.238)\text{Men}$$

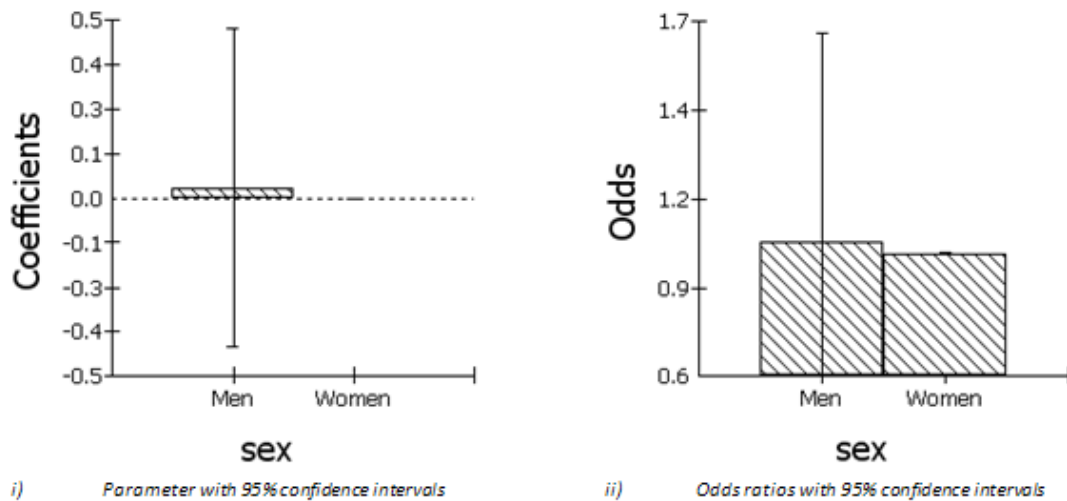


Figure 12.12: Univariate model i) coefficients and ii) incidence rate ratios: sex (lost to follow-up)

In terms of whether men were more likely to be lost to follow-up or not, the positive coefficient (0.032) suggested that this might indeed be the case, though very weakly (odds ratio of 1.032). However, the relatively large standard error and generously overlapping 95% confidence intervals either side of baseline suggests that there is no significant differential between men and women.

### 7.7.3 Age

$$\text{lost}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$
$$\text{logit}(\pi_i) = 0.330(0.443)\text{cons} + -0.035(0.013)\text{age}$$

Older patients were more likely to utilise their referral to the HCV specialist centre, and in this case were also more likely to keep to their follow-up appointments as the coefficient (-0.035). The association had a low standard error (0.013) which indicates statistical significance (p-value: 0.005).

### 7.7.4 Deprivation

$$\text{lost}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$
$$\text{logit}(\pi_i) = -1.165(0.147)\text{cons} + 0.110(0.034)\text{carstair2}$$

Socioeconomic position has been previously argued to be a strong predictor of healthcare utilisation. Although the measure of socioeconomic deprivation did not appear to have any effect of significance upon the likelihood of first appointment attendance, the positive coefficient in this univariate model indicates a strong association with continued follow-up. More specifically, for a one unit increase in the level of socioeconomic deprivation, the likelihood of being lost to follow-up increases by 0.110 in the log of the odds. Since the standard error is relatively small (0.034), this association is also highly significant (p-value: 0.001).

### 7.7.5 IDU history

$$\text{lost}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -1.460(0.231)\text{cons} + 0.788(0.264)\text{Injected}$$

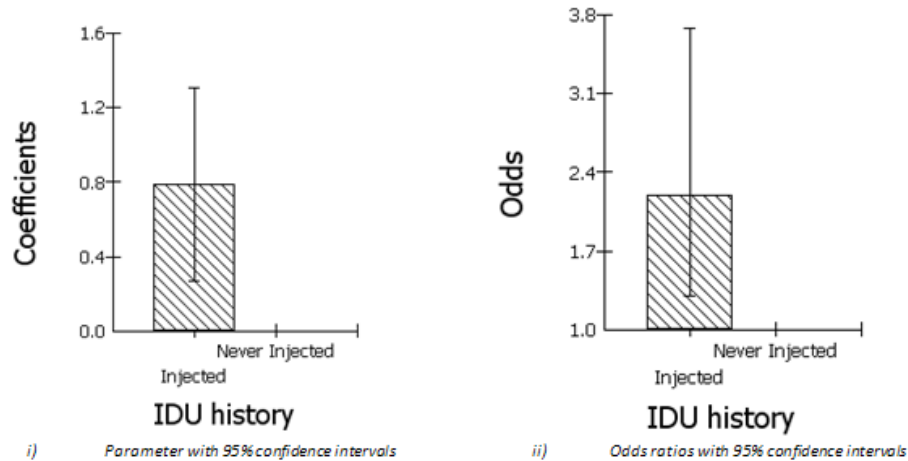


Figure 12.13: Univariate model i) coefficients and ii) incidence rate ratios: IDU history (lost to follow-up)

A history of IDU was strongly associated with a decreased likelihood of utilising the referral appointment. For those individuals that did, a history of IDU continued to be of significance, positively associated with the chances of being lost to follow-up (coef: 0.788). To aid interpretation, the odds ratio indicates that individuals with a history of IDU were 2.199 times (Figure 12.14) more likely to be lost to follow-up than those without. The relatively small standard error (0.064) and 95% confidence intervals contained above baseline indicate a highly significant association (p-value: 0.003).



## 7.7.6 Travel-time

$$\text{lost}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -0.574(0.278)\text{cons} + -0.123(0.102)\text{loghcvt}$$

$$\text{lost}_i \sim \text{Binomial}(\text{cons}_i, \pi_i)$$

$$\text{logit}(\pi_i) = -0.749(0.238)\text{cons} + 0.095(0.339)\text{ttq2} + -0.075(0.338)\text{ttq3} + -0.471(0.358)\text{ttq4} + -0.254(0.345)\text{ttq5}_i$$

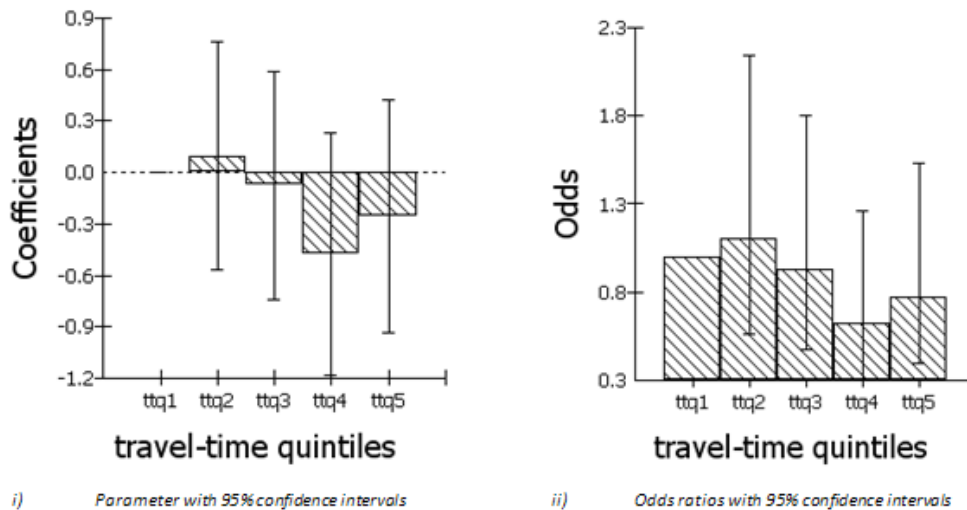


Figure 12.14: Univariate model i) coefficients and ii) incidence rate ratios: travel-time to specialist (lost to follow-up)

As with all previous analyses, the travel-time measure is the main explanatory test variable. Expressed in a continuous format, the univariate model yielded a negative coefficient (-0.123), counterintuitive to the hypothesised influence as it appeared that individuals with poorer geographic access were more likely to keep up with appointments. The relatively large standard error, however, pointed towards the statistical insignificance of this association (p-value: 0.230). Again, it was very possible that the influence of travel-time would be experienced disproportionately amongst those individuals living furthest away from the specialist centre, so the effect may be

non-linear and threshold-like. A second univariate model was fitted, substituting the continuous travel-time measure for the quintiles. A reasonably consistent negative gradient was observed (the inverse of the hypothesised effect), though with all 95% confidence intervals overlapping the baseline none of these coefficients were statistically significant.

## **7.8 Multivariate associations (lost to follow-up)**

Table 12.16 illustrates the results of a binary logistic regression modelling long-term follow-up, with explanatory variables added in sequentially. In Model 8, there is the familiar univariate non-association between men relative to women. Adding in the age variable for Model 9 demonstrates a statistically significant, negative, association with the likelihood of being lost to follow-up sensu the univariate model (coef: -0.035; p-value: 0.005). The age association and its significance level is attenuated (coef: 0.095; p-value: 0.027), however, by the inclusion of the socioeconomic deprivation variable (Model 10). The deprivation coefficient is positive (0.095) and highly significant (p-value: 0.007) as seen in the univariate model.

Adjusting these covariates for the IDU history differential (Model 11), which itself suggested a strong coefficient but only marginally significant (coef: 0.554; p-value:

0.048), had an attenuating effect on deprivation (coef: 0.088; p-value: 0.013) and negated the men/women differential to practically zero. Notably, the magnitude of the age coefficient decreases slightly, but the statistical significance is fully negated (p-value: 0.117). These effects remove any lingering suspicion that men may be more likely to be lost to follow-up, whilst also suggesting that IDU history is associated with age and socioeconomic deprivation, reflecting findings in the literature (Craine, Walker, Carnwath, and Klee 2004; Hutchinson et al. 2004).

The main explanatory test variable, travel-time was added to the Model (12) in continuous format. The statistically insignificant negative coefficient (-0.036; p-value: 0.740) resembled the association found by the univariate model and made little difference to the covariates. The same cannot quite be said of Model 13, in which the continuous measure of travel-time is substituted for quintiles. Unlike the (insignificant) negative association found for the continuous measure and in the univariate model with quintiles, these travel-time coefficients were positive after controlling for the other covariates. Hence, the direction of association fits the hypothesis in that those individuals with further to travel are more likely to be lost to follow-up or discontinued utilisation. However, the standard errors are relatively large, the magnitude of the coefficients not strong, the direction of association not consistently positive as quintile 3 is actually negative, and none of the coefficients were even marginally statistically significant.

Overall, it seems, the risk of being lost to follow-up in long-term utilisation of an HCV specialist centre cannot be attributed to how far an individual is generally required to travel. However, it was appreciated within the earlier review of the literature that long journey times and distances are likely to be perceived differently in terms of affordability and acceptability by different groups. Older individuals may be one group in particular that is likely to have reduced mobility through a lack of access to private transport or shorter commuting tolerances. With this in mind, an interaction term was fitted between age and each of the travel-time quintiles under the hypothesis that older patients living further from the specialist HCV centre would be more likely to be lost to follow-up. The results displayed in Model 14 are somewhat surprising, with some reflection a trend that was hinted at in earlier analyses. It appears that patients that were diagnosed at an older age and with what has been so far considered as ‘poor’ geographic access, are actually less likely to be lost to follow-up than those living closer to the HCV specialist centre. Figure 12.15 illustrates these findings, with each coefficient from quintiles 3-5 significantly below baseline as demonstrated by the 95% confidence intervals, though the overlapping with each other means that a dose-response association is not evident.

Table 12.4: Multivariate logit regression model: model 14 is the fully adjusted version (equation also shown)

$$\text{logit}(\pi_i) = -3.416(1.238)\text{cons} + 0.013(0.252)\text{Men} + 0.054(0.033)\text{age}_i + 0.085(0.039)\text{carstair}_i + 0.600(0.287)\text{injected}_i + 2.146(1.501)\text{ttq}_i + 4.669(1.719)\text{ttq}_i + 3.307(1.593)\text{ttq}_i + 2.981(1.485)\text{ttq}_i + 0.057(0.042)\text{ttq}_i + 0.051(0.045)\text{ttq}_i + 0.101(0.045)\text{ttq}_i + 0.087(0.042)\text{ttq}_i + 0.045\text{age}_i$$

	Model 8	Model 9	Model 10	Model 11	Model 12	Model 13	Model 14															
	Coefficient	Coefficient	Coefficient	Coefficient	Coefficient	Coefficient	Coefficient															
	Standard Error	Standard Error	Standard Error	Standard Error	Standard Error	Standard Error	Standard Error															
	p-value	p-value	p-value	p-value	p-value	p-value	p-value															
Constant	-0.905	0.198	<0.001	0.301	0.468	0.520	-0.165	0.504	0.744	-0.773	0.596	0.195	-0.674	0.666	0.311	-0.789	0.650	0.225	-3.416	1.238	0.006	
Sex ( <i>base: women</i> )																						
Men	0.032	0.238	0.894	0.047	0.241	0.847	0.051	0.243	0.835	0.001	0.245	0.997	0.004	0.245	0.987	0.023	0.247	0.924	0.013	0.252	0.959	
Age				-0.035	0.013	0.005	-0.029	0.013	0.027	-0.022	0.014	0.117	-0.022	0.014	0.117	-0.022	0.014	0.113	0.054	0.033	0.101	
Deprivation							0.095	0.035	0.007	0.088	0.036	0.013	0.084	0.037	0.022	0.082	0.038	0.030	0.085	0.039	0.028	
IDU history ( <i>base: never injected</i> )							0.554	0.280	0.048	0.556	0.280	0.047	0.553	0.281	0.049	0.600	0.287	0.037				
Injected																						
Travel-time to specialist centre ( <i>log</i> )																						
Travel-time quintiles ( <i>base: quintile 1</i> )																						
Quintile 2																						
Quintile 3																						
Quintile 4																						
Quintile 5																						
Travel-time quintiles*age interaction ( <i>base: quintile 1</i> )																						
Quintile 2*age																						
Quintile 3*age																						
Quintile 4*age																						
Quintile 5*age																						
N (referred patients)	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	
n (not-attended)	117	117	117	117	117	117	117	117	117	117	117	117	117	117	117	117	117	117	117	117	117	
Pseudo R2	<0.001	0.017	0.033	0.041	0.041	0.041	0.041	0.041	0.041	0.041	0.041	0.041	0.041	0.041	0.041	0.041	0.041	0.041	0.041	0.041	0.041	
Log likelihood	-241.741	-237.575	-233.877	-231.830	-231.775	-231.775	-231.775	-231.775	-231.775	-231.775	-231.775	-231.775	-231.775	-231.775	-231.775	-231.775	-231.775	-231.775	-231.775	-231.775	-231.775	
LR chi2	0.020	8.350	15.750	19.840	19.950	19.840	19.840	19.840	19.950	19.840	19.950	19.840	19.840	19.840	19.950	19.840	19.840	19.840	19.840	19.840	19.840	
Prob > chi2	0.894	0.015	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	

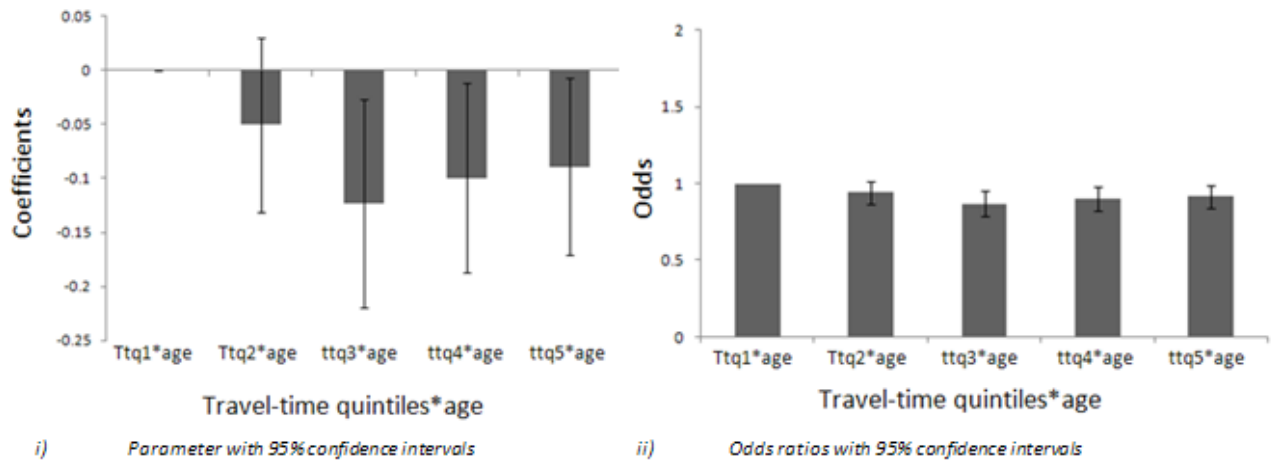


Figure 12.15: Multivariate model i) coefficients and ii) incidence rate ratios: travel-time to specialist\*age (lost to follow-up)

## 7.9 Discussion

There is a concern amongst policy makers that many persons diagnosed with HCV infection in Scotland fail to reach and stay within HCV specialist care services (Parkes, Roderick, Bennett-Lloyd, and Rosenberg 2006; The Scottish Government 2008). Some studies have explored variation in awareness and patterns across population dichotomies (e.g. men/women, IDU/non-IDU). However, less attention has been placed on whether how far a person must travel effects utilisation. In a region of Scotland that encompasses sparsely populated remote areas as well as urban, the analyses in this chapter have demonstrated that patients travelling further do not seem to be any less likely to attend their first appointment, nor more likely to be lost to follow-up than those living closer.

Overall, these results would suggest that geographic access is generally not a particularly important factor influencing the low rates of attendance and long-term follow-up. Thus, improving geographic access (e.g. more evenly-spatially distributed specialist centres) is unlikely to solve the problem in this case. However, there are two important notes of caution for the interpretation of these results. Firstly, in this particular study population the level of patient utilisation of the HCV specialist centre was actually quite high (85.7% attended their first appointment, 70.8% of those that attended were classified as adhered) compared with the 50% suggested for Scotland as a whole (The Scottish Government 2008). Though we have no information for any other HCV specialist centre in Scotland, this could indicate that GPs and HCV-related medical staff in NHS Tayside are performing particularly well in conveying the importance of attending the referral and subsequent follow-up to patients.

Secondly, and in relation to the first, an interesting result was uncovered, in that older patients with further to travel were more likely to stay in follow-up comparing to those with more favourable geographic access to the specialist centre. Although a similarly odd finding was found in a study by Crawford and colleagues, in which patients diagnosed with certain cancers and with further to travel to a specialist cancer centre were also more likely to have utilised treatment than those living in closer proximity. Their suggestion for this association was the difficulty of providing healthcare in more deprived areas, which are typically located nearby specialist cancer centres (Crawford et al. 2007). This explanation may also apply to the results in this chapter, whereby the

use of an ecological measure of socioeconomic deprivation may not sufficiently adjust for the disadvantage suffered by some patients, despite their relatively favourable geographic access to the specialist HCV centre.

However, another important and equally valid explanation is that the data used in this thesis is very likely to suffer selection bias. It might be that those individuals most likely to be disadvantaged by having to travel long distances and journey times have not even been diagnosed, with previous studies of HCV detection suggesting lower rates amongst populations lacking geographic access to primary healthcare (Monnet et al. 2006; Monnet et al. 2008). The earlier study in this thesis, however, suggests that we cannot be absolutely sure of this observation yet. Rather more likely, it is the selectivity that occurs at the point of diagnosis when a GP decides to refer their patient. Geographic access to a specialist was shown to be associated with a decreased likelihood of referral in the previous chapter. With similar trends for patients with and without a history of OST (i.e. a medically-known history of IDU), it seemed that a lack of awareness amongst GPs of referral protocol (that is, to refer all patients with chronic HCV) was the most probable explanation. Perhaps then, those patients that were referred from less aware GPs were more demanding of referral and in more affluent circumstances and motivated to be able to cope with travelling long journey times. In contrast, perhaps those patients that were not referred may be those that would have struggled with the lack of geographic access, less motivated toward health-seeking behaviour, harbouring more fatalistic attitudes towards health and healthcare. This leaves the Clinical data



skewed towards younger individuals with a history of IDU, who are often resident in socioeconomically deprived areas relatively close to the HCV specialist centre, and also towards older patients living further away but with the socioeconomic resources to be able to cope with frequent visits over long travel-times.

Therefore, it means that it would be wrong to dismiss geographic access at this moment. It could very well be that those persons absent are precisely those that are likely to suffer most from a lack of geographic accessibility (e.g. the elderly and single parents). Furthermore, as the undiagnosed and unreferred population infected with HCV age, they will be at greater risk of symptoms associated with the latter stages of chronic HCV infection including: debilitating fatigue; cognitive dysfunction; depression; and a reduced overall quality of life (Brienza et al. 2000; Brooner et al. 1997; Callaly, Trauer, Munro, and Whelan 2001; Cordoba et al. 2003; Dunne and Quayle 2002; Foster, Goldin, and Thomas 1998; Golden, O'Dwyer, and Conroy 2005; Mason et al. 1998; Rodger et al. 1999; Spiegel et al. 2005). Older patients are also more vulnerable to developing serious liver-related complications of cirrhosis and hepatocellular carcinoma (Giacosa and Hill 1996; Ince and Wands 1999; Perz and Alter 2006; Perz et al. 2006). As HCV education becomes more widespread amongst the public and medical professionals and rates of detection improve, it is likely that a larger number of older patients presenting with HCV-related symptoms and liver-complications will be referred to specialist centres. For those patients resident in remote, rural areas, the challenge of travelling long distances frequently, amplified by HCV-related morbidity, is likely to be more difficult

than for the few that were observed in this study. The significant interaction between age and long travel-times in this study could be a glimpse of what may become more commonly observed over the next decade of HCV research. Where a person lives could become a very important factor for the delivery of HCV-related healthcare and appropriate measures should be taken to ensure that when more people are referred, how far they need to travel is not going to influence whether they receive healthcare.

As for the other findings in this thesis, we found no significant gender bias towards either outcome, despite previous research suggesting women to be more likely to seek healthcare than men in the context of HCV (Gisbers van Wijk, van Vliet, and Kolk 1996; Temple-Smith et al. 2007). As several studies have also noted previously (Bini et al. 2005; Butt, Justice, Skanderson, Rigsby, Good, and Kwoh 2007; Butt, Wagener, Shakil, and Ahmad 2005; Temple-Smith et al. 2007), a history of IDU was an important predictor of non-attendance. It has been suggested that patients with a history of IDU may have a poorer understanding of HCV (Davis, Rhodes, and Martin 2004; Davis and Rhodes 2004) and may lack a trusting relationship with their GP who could help them endure the difficulties of HCV treatment (Edlin 2004). However, IDU was a significant predictor of loss to follow-up and it is difficult to conclude whether this is due to good performance by medical staff or selection bias in the study population. For long-term follow-up, patients that were exposed to greater levels of socioeconomic deprivation were more likely to be lost to follow-up (Seal, Currie, Shen, Anand, Bini, Brau, Jeffers, and Wright 2007). This suggests that keeping up with appointments may be difficult for

patients occupying less favourable socioeconomic positions, who often lack poorer access to material and financial resources, experience longer periods of unemployment and are at greater risk of morbidity and psychological distress.

Finally, it is important to appreciate that the travel-times used in this thesis underestimate the true remoteness of some individuals in NHS Tayside. These estimates do not include the duration of the appointment itself, or how long it takes to travel using public transport, both of which might enhance our knowledge of how patients account for geographic access into their decision-making. Further developments in GIS tools and data resources on public transport availability, frequency and expense may provide a more rounded picture in future studies. A lack of data on dates of first and follow-up appointments removed the possibility of time-series analyses and there was no information available on why patients did not attend or were lost to follow-up. The absence of detailed and reliable HCV data from other regions restricted focus to NHS Tayside which with small numbers limited the statistical power of the study. However, the emergence of such data on a national scale would be useful for more sophisticated follow up research if available.

## **7.10 Summary**

### **7.10.1 What we knew before?**

Not all persons infected with HCV in Scotland have been diagnosed. All patients that are diagnosed are meant to have been referred to their nearest HCV specialist centre, but not all are. Even of those that are referred, not everyone utilises this opportunity. And of those that do, some discontinue utilisation or are lost to follow-up at some point after. Of the latter two situations, few studies in Scotland have explored factors that might contribute to the under-utilisation of specialist HCV centres. No study has explored the potential influence of geographic accessibility, despite numerous other studies showing significant associations with the utilisation of specialist healthcare centres.

### **7.10.2 What this study has contributed?**

The analyses presented in this chapter used logistic regression models to investigate potential influences of travel-time to a specialist HCV centre on the likelihood of utilising : i) the first referral appointment; and ii) long-term follow-up, adjusting for covariates. Patients with further to travel were no less likely to attend, nor more likely

to be lost to follow-up than those living closer. However, there was evidence of an interaction between age and travel-time, with loss to follow-up less likely for older people with further to travel comparing with those with more favourable geographic access. Selection bias in the study sample and the difficulty of providing healthcare to more deprived populations resident nearby the specialist centre are two potential explanations for this trend. Additionally, IDU history predicted non-attendance, whereas socioeconomic deprivation was associated with loss of follow-up. Older age was a significant predictor of first-appointment attendance only.

### **7.10.3 What gaps remain?**

As more of the undiagnosed infected population are detected, as a greater number of patients are referred, and as levels of HCV-related morbidity increase, geography may yet become a significant issue for policy. Follow-up studies of HCV specialist centre utilisation in NHS Tayside and other healthboards are thus advisable.

# **8. Are individuals with poorer geographic access to healthcare more likely to suffer liver-related mortality outcomes?**

## **8.1 Introduction**

In chapters so far, the influence of geographic access to healthcare, primary and specialist, on HCV-related outcomes has been mixed. Rates of detection amongst populations with further to travel to their nearest GP were low after adjusting for covariates, though only for patients with a history of OST, who are perhaps more likely to live in more urban areas anyway (raising suspicion of selection bias). Patients living furthest from the HCV specialist centre were less likely to be referred, irrespective of a history of OST, suggesting factors other than IDU-discrimination may be influential. Of those patients that were referred, most attended their first appointment and a large

proportion stayed in follow-up, with geographic access not playing any significantly detrimental role in utilisation.

However, as discussed, the high selectivity of the latter study population probably meant that the most affluent and mobile patients in more remote areas who were able to cope with the rigours of long travel-times had been referred. Indeed, other studies have suggested that communication and acceptability of healthcare is likely to vary, with more affluent individuals demanding more access.

Reflecting on a previous discussion of what makes an appropriate referral, it seems that in the context of HCV (where, incidentally, the problem is under-referral and not over-referral), that the more important outcome to measure is of those patients that were not referred (Dowie 1983). Although taking into account the small number of individuals that died shortly after being diagnosed with HCV did not have a significant influence upon overall trends of referral observed, there may be unobserved issues at hand. For instance, are individuals lacking geographic access to healthcare more likely to be diagnosed later, with more advanced presentation of symptoms? Numerous studies have suggested that individuals lacking geographic access to healthcare may be at greater risk of being diagnosed late, reducing the odds of survival (Haynes, Pearce, and Barnett 2008; Jones et al. 2008b; Kim, Gatrell, and Francis 2000). If so, does this explain the travel-time-decay effect in the likelihood of referral to an HCV specialist centre found in a previous chapter?

Unfortunately, in this data there is no extra information on the stage of HCV progression at diagnosis so it is difficult to ascertain the degree to which an individual was diagnosed 'early' or 'late'. However, the longer a person goes undetected with HCV infection, the greater the risk of developing cirrhosis and liver cancer (hepatocellular carcinoma) and the increasing risk of death from liver-related causes (Alberti, Chemello, and Benvegnu 1999; Alter et al. 1992; El-Serag, Davila, Petersen, and McGlynn 2003; Poynard, Bedossa, and Opolon 1997). Hence, mortality from liver-related causes in a population infected with HCV might offer a crude surrogate of disease severity upon detection.

The objective of this chapter is to explore the association between geographic access to primary and specialist healthcare and liver-related mortality, with close attention to patients that were and were not referred. Mortality from all-causes and drugs-related causes are also considered for indirect comparisons.

## **8.2 Methodological approach**

In attempting to measure whether geographic access to healthcare influences the chances of survival, Ordinary Least Squares (OLS) modelling is inappropriate (Hosmer, Lemeshow, and May 1999). The problem with OLS is with the assumed normality distribution of the residuals. Hence, this would imply the time to an event occurring (e.g.



death) would have to follow a normal distribution. However, in terms of the time from diagnosis to death, as is the objective of this chapter, this assumption is flawed. For instance, some patients are diagnosed at a very early stage of infection and could live a long time before death occurs, if at all. On the other hand, many patients may die shortly after being diagnosed because they presented with advanced stages of liver disease. In studies of survival with access to individual-level data, a common methodological approach is to reject OLS in favour of Cox's proportional hazard model, commonly referred to simply as the 'Cox model' (Cleves, Gould, Gutierrez, and Marchenko 2008; Cox 1972).

At its simplest, the Cox model allows the estimation of association between the probability of a death occurring and explanatory variables, but without necessitating any assumptions about the shape of the baseline hazard function (Satagopan, Ben-Porat, Berwick, Robson, Kutler, and Auerbach 2004). From baseline (e.g. diagnosis), a patient is followed over a specified unit of time (e.g. months) until the outcome of interest occurs (e.g. death). An advantage of the Cox regression over other forms of survival analysis (e.g. Kaplan Meier) is the ability to analyse a 'treatment' effect on survival with adjustment for other factors such as age, sex, stage of disease or any other covariate (the Kaplan Meier approach cannot be used to explore and adjust for several explanatory variables simultaneously within a single model, which creates difficulty of interpreting association and confounding) (Cleves, Gould, Gutierrez, and Marchenko 2008).

Cox regression has been utilised in some studies similar to that proposed in this chapter. For instance, in England, Kim and colleagues used this approach to estimate influences of place on the post-surgery survival of patients diagnosed with colorectal cancer. Adjusting the model for age, gender, site of the tumour, disease stage at the time of operation, hospital size and the surgery type, Kim and colleagues found that the district in which surgery took place had an influence upon survival (though in unadjusted models, socioeconomic deprivation and distance from residence to hospital were also significant) (Kim, Gatrell, and Francis 2000). Also in England, Jones and colleagues used Cox models to investigate the influence of geographic access to primary and secondary healthcare on survival from particular types of cancer (Jones et al. 2008b). Although survival was shorter for patients with prostate cancer who had further to travel to consult their nearest GP, measures of geographic access to tended to show little consistent association with survival from other types of cancer. Similar findings resulted from a study in New Zealand by Haynes and colleagues, also finding poorer chances of survival amongst men with prostate cancer living far from a GP and also of individuals with colorectal, breast and prostate cancer with further to travel to a specialist cancer centre (Haynes, Pearce, and Barnett 2008).

## **8.3 Study specification**

### **8.3.1 Study sample and setting**

The data used in the following analyses included all anti-body positive HCV diagnosed patients in the ELDIT that featured in chapter 5 and 6. Each patient was at least 15 years old and had full age, sex, and 2001 Census Output Area of residence data. Patients diagnosed whilst in prison and those resident in Output Areas outside of NHS Tayside were omitted for reasons previously discussed. Because the methodological approach was to utilise a Cox model, the data was left unaggregated at an individual-level.

As in every other chapter so far, the study context is NHS Tayside, where the contrasting levels of geographic accessibility to primary healthcare and the specialist HCV centre make it an interesting area for studies of this type.

### **8.3.2 Variable definition**

The response variable in the following Cox models took the form of a dichotomous variable: (1) death from any cause; (0) not dead by the end of the study. Information on patients date of diagnosis and date of death (where relevant) were used to calculate

survival times in months. For patients that remained alive to the end of the study period (31<sup>st</sup> December 2003), the equivalent number of months was calculated (right censoring). In addition to all-cause mortality, two other cause-specific dichotomous response variables were defined: i) liver-related; and ii) drugs-related. The latter were based upon the International Classification of Diseases (ICD) 10th revisions (corresponding to years 2000-2005) for the primary cause of death, using the same method of classification employed by Amin and colleagues study of HCV infection and cause-specific mortality (Amin, Law, Bartlett, Kaldor, and Dore 2006). Patients with deaths classified using ICD-9 codes (1980-1999) were mapped to the ICD-10 classification using a publicly available look-up table (New Zealand Ministry of Health Information Service 2008).

As in chapters 5 and 6, a history of OST was identified from prescriptions data held within the ELDIT, identifying patients with a history of IDU known to the medical profession. A dichotomous variable identifying whether a patient was referred to an HCV specialist centre or not was also included to explore survival outcomes for those that were not referred by their GP relative to those that were. The Carstairs index was used as a measure of socioeconomic deprivation to identify socioeconomic position in the absence of individual measures.

Geographic access to primary healthcare and the HCV specialist centre were used as the main explanatory test variables, following on from the studies by Jones et al and Haynes

et al, both variables of which having already been defined and utilised in previous chapters.

### **8.3.3 Analysis specification**

Associations between all-cause and cause-specific mortality and each explanatory variable were explored in separate univariate Cox regression, followed by fully adjusted multivariate models per response. To control for the competing risks of death from liver-related, drugs-related or any other cause, individuals that died because of a cause that was not the response variable of interest were omitted (i.e. in models of liver-related mortality, patients that died from non-liver-related causes were not analysed). This approach thus does not treat the different types of death jointly which complicates comparisons between model coefficients (Lunn and McNeil 1995; Putter, Fiocco, and Geskus 2007), though the main focus is to explore associations with each cause separately and only indirect comparisons across models. For modelling purposes, the travel-time measure was calculated as natural logarithm to reduce problems of skewness. Non-linear associations were not appropriate due to the small numbers in each response variable.

## 8.4 Descriptives

Cause of death (ICD-10 code)		#	%
Liver-related (K70; C22; K71-K77; B9462; B15-B19)		28	15.9
Liver-related causes by category	Alcoholic liver disease (K70)	5	2.8
	Liver cancer (C22)	10	5.7
	Non-alcoholic liver disease (K71-K77)	6	3.4
	Sequale of viral hepatitis (B9462)	1	0.6
	Viral hepatitis (B15-B19)	6	3.4
Drugs-related (F1-F16; F19; F55; X40-X44; X60-X64; X85; Y10-Y14)		34	19.3
Not drugs or liver-related		114	64.8
Total number of deaths			176
Total patients surviving			714
Total patients			890

**Table 13.1: Classified causes of death, by time of death**

Of the 890 patients diagnosed with HCV, 176 (19.8%) died from all causes before the end of the study period. Table 13.1 reports the classification of these deaths according to a previously published approach (Amin et al. 2006). Deaths from non-liver-non-drugs-related causes were most prevalent at 64.8%, with deaths from drugs-related and liver-related causes at 19.3% and 15.9% respectively. Liver-related causes of death were fairly evenly spread, though liver cancer (hepatocellular carcinoma) was particularly high at 5.7% and sequale of viral hepatitis (death from the acute stage of infection) was rare at 0.6%. The very small numbers of each type of liver-related cause rendered further disaggregated investigation unreliable.

Table 13.2 describes the study population characteristics for those patients that died from i) all-causes; ii) liver-related causes; and iii) drugs-related causes. In all three groups, far more men than women died. Whilst the mean age of all-cause mortality was 45.3, the mean age of liver-related cause mortality was much higher than those of drugs-related causes, at 52.0 and 33.3 respectively. This is reassuring given the higher prevalence of IDU amongst younger age groups and what is known of the natural history of HCV and the greater likelihood of developing liver-related complications in older age.

Characteristic	All-cause		Liver-related		Drugs-related	
Males (#, %)						
<i>Female</i>	48	27.3	5	2.8	6	3.4
<i>Male</i>	128	72.7	23	13.1	28	15.9
Mean age (min - max)	45.3	(19-91)	52.0	(28-83)	33.3	(21-54)
Opiate substitution therapy (#, %)						
Yes	66	37.5	5	2.8	26	14.8
No	110	62.5	23	13.1	8	4.5
Referred to specialist (#, %)						
Yes	16	9.1	5	2.8	5	2.8
No	160	90.9	23	13.1	29	16.5
Mean deprivation (min-max)	2.1	(-3.8-10.6)	1.6	(-3.8-8.41)	2.8	(-2.2-7.9)
Mean travel-time to primary healthcare (min-max)	3.4	(0-11)	3.6	(0-11)	2.7	(0-10)
Mean travel-time to specialist (min-max)	18.1	(0-72)	16.8	(2-62)	16.4	(0-72)
Mean months survival (min-max)	37.83523	(0-155)	41.00	(0-134)	35.82	(0-106)

**Table 13.2: Characteristics of the study population, by cause of death**

For all-cause mortality, individuals without a history of OST outnumbered those with (62.5% to 37.5%) and clear differences were again evident between the cause-specific groups. Unsurprisingly, most individuals suffering a drugs-related death had a history of OST (n=26, to only 8 that did not). Only 5 individuals who died from liver-related causes had a history of OST, to 23 that had not.

Interestingly, the vast majority (91%) of individuals that died from all-causes had not been referred, with only 16 that had. Similar trends were found amongst both of the cause-specific groups, with only 5 of 28 and 5 of 34 individuals referred who subsequently died from liver-related and drugs-related causes respectively.

Mean socioeconomic deprivation was fairly high (2.1) amongst those that died from all-causes. Deaths from liver-related causes occurred in less deprived areas on average (1.6), whereas the obverse was found for drugs-related deaths (2.8).

Little mean variation was found between travel-times to the nearest GP and the HCV specialist centre. Average travel-times to GP were 3.4 minutes for deaths from all-causes, marginally longer (3.6) for liver-related and shorter (2.7) for drugs-related causes. The longest travel-time to the nearest GP was reported at 11 minutes, whereas it was 72 minutes for the HCV specialist centre. Mean travel-times to the latter for individual deaths from all-cause was 18.1 minutes, slightly lower for liver-related causes at 16.8 minutes, and lower still for drugs-related causes at 16.4 minutes. These results do not look to support the overall hypothesis, that was liver-related causes would be



more geographically spread relative to those from drugs-related causes. In terms of the mean number of months survived following diagnosis, the figure for all-causes was 37.8 months, 41.0 months for liver-related causes and 35.8 months for drugs-related causes. Since there were so few cause-specific deaths, it would not have been appropriate to further classify by discrete time periods to distinguish deaths shortly after diagnosis from those occurring later.

## 8.5 Univariate associations

Univariate Cox regression models of each separate response and explanatory variable are displayed in Table 13.3. Hazard ratios above 1 indicate positive association between the explanatory variable and the risk of mortality, whereas below 1 suggests negative association. Standard errors and p-values are given *sensu* previous chapters.

Mortality from all-causes, liver-related causes or drugs-related causes did not seem to significantly differentially effect men more than women overall, though hazard ratios above 1 implied this possibility. Individuals diagnosed in older age were at greater risk of death from all-causes (hazard ratio: 1.047, p-value: <0.001) and slightly more so from liver-related causes (hazard ratio: 1.092, p-value: <0.001) as would be expected. Older

age was not a significantly associated with drugs-related mortality, with the direction of effect suggested that younger persons were at greater risk.

	Model 1 (all-cause)			Model 2 (liver-related)			Model 3 (drugs-related)		
	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value
Sex ( <i>base: women</i> )									
Men	1.088	0.192	0.634	1.770	0.881	0.252	2.035	0.997	0.147
Age	1.047	0.005	<0.001	1.092	0.013	<0.001	0.989	0.021	0.949
Opiate substitution therapy ( <i>base: no</i> )									
Yes	0.716	0.118	0.043	0.225	0.123	0.006	3.540	1.534	0.004
Referred to specialist ( <i>base: yes</i> )									
No	6.835	1.858	<0.001	3.519	1.753	0.012	3.887	1.905	0.006
Deprivation (continuous)	0.996	0.024	0.885	0.968	0.059	0.597	1.040	0.060	0.499
Travel-time to primary healthcare (log)	1.011	0.094	0.910	1.208	0.288	0.427	0.796	0.156	0.244
Travel-time to specialist (log)	0.851	0.062	0.027	0.866	0.155	0.421	0.697	0.115	0.028
N (patients)	871			734			738		
# deaths analysed	163			26			30		
Times at risk	47284			41773			41843		

**Table 13.3: Univariate associations between survival and explanatory variables: Cox proportional hazard models**

The OST differential displayed interesting univariate trends, for those that had a history of OST were very strongly likely to die from drugs-related causes (hazard ratio: 3.540, p-value: 0.004), but also strongly unlikely to die from liver-related causes (hazard ratio: 0.225, p-value: 0.006), with the hazard ratio for all-cause mortality also sitting negative but with weak statistical significance (hazard ratio: 0.716, p-value: 0.043). These trends were partially expected from the earlier descriptive observations. Likewise, for the referral binary, all individuals that were not referred to the HCV specialist centre were at much higher risk of all-cause (hazard ratio: 6.835, p-value: <0.001), liver-related (hazard

ratio: 3.519, p-value: 0.012) and drugs-related (hazard ratio: 3.887, p-value: 0.006) cause mortality.

In contrast to the aforementioned strong associations, neither socioeconomic deprivation nor travel-time to the nearest GP were statistically significantly associated with any type of mortality, though the direction of effect for individuals suffering all-cause ((hazard ratio: 1.011) and liver-related (hazard ratio: 1.208) causes of death was in the hypothesised (positive) direction. Travel-time to the HCV specialist centre was significantly negatively associated with the risk of death from all-cause (hazard ratio: 0.851, p-value: 0.027) and more strongly for drugs-related causes (hazard ratio: 0.697, p-value: 0.028). The number of deaths analysed relative to the study population are listed at the bottom of Table 13.3, with smaller numbers because of omitted deaths and censored individuals occurring within 1 month of diagnosis.

## **8.6 Multivariate associations**

Multivariate Cox regression models for the same response variables were used to explore the consistency of the univariate trends. Again, men were not at significantly greater risk of mortality compared to women. The effect of older age increasing the risk of all-cause (hazard ratio: 1.048, p-value: <0.001) and liver-related cause (hazard ratio:

1.092, p-value: <0.001) mortality persisted, whereas the univariate negative association for drugs-related mortality was inverted but remained insignificant.

	Model 4 (all-cause)			Model 5 (liver-related)			Model 6 (drugs-related)		
	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value
Sex ( <i>base: women</i> )									
Men	0.975	0.175	0.887	1.850	0.946	0.229	1.601	0.797	0.344
Age	1.048	0.006	<0.001	1.092	0.015	<0.001	1.016	0.024	0.497
Opiate substitution therapy ( <i>base: no</i> )									
Yes	1.366	0.280	0.128	0.623	0.392	0.452	3.802	1.823	0.005
Referred to specialist ( <i>base: yes</i> )									
No	5.703	1.566	<0.001	3.379	1.743	0.018	3.794	1.875	0.007
Deprivation (continuous)	1.028	0.028	0.320	1.068	0.070	0.314	0.958	0.062	0.506
Travel-time to primary healthcare (log)	0.955	0.093	0.632	0.959	0.238	0.865	0.906	0.197	0.651
Travel-time to specialist (log)	0.780	0.064	0.002	0.721	0.161	0.143	0.704	0.120	0.040
N (patients)	871			734			738		
# deaths analysed	163			26			30		
Times at risk	47284			41773			41843		
log pseudolikelihood	-900.361			-119.616			-167.535		
LR chi2	163.930			60.790			26.930		
Prob > chi2	<0.001			<0.001			<0.001		

**Table 13.4: Multivariate associations between survival and explanatory variables: Cox proportional hazard models**

Mortality from drugs-related causes continued to be strongly positively associated with a history of OST (hazard ratio: 3.802, p-value: 0.005). However, after adjusting for covariates the negative associations for all-cause and liver-related cause mortality were rendered statistically insignificant. Interestingly, the direction of effect for all-cause mortality was changed from negative to positive.

The strong univariate association between referral and mortality continued, albeit attenuated, after adjustment for covariates. The effect appeared strongest in the all-cause mortality group (hazard ratio: 5.703, p-value: <0.001), but also high for liver-related (hazard ratio: 3.379, p-value: 0.018) and drugs-related causes (hazard ratio: 3.794, p-value: 0.007).

Deprivation was not a statistically significant predictor of mortality, nor was travel-time to the nearest GP. Travel-time to the HCV specialist centre was negatively associated with all-cause mortality (hazard ratio: 0.780, p-value: 0.002) and drugs-related causes (hazard ratio: 0.704, p-value: 0.040). A negative hazard ratio was also reported for liver-related causes of mortality (0.721), but was statistically insignificant. Interaction terms fitted to test association between referral outcome, geographic access to healthcare and mortality were not significant.

## **8.7 Discussion**

The analyses set out in this chapter were aiming to identify the extent that a lack of geographic access to healthcare, primary and specialist, might be associated with liver-related causes of mortality. Late detection increases the risk of liver-related causes of death and it could be that patients with further to travel might be at greater risk of

being diagnosed later. In fact, no significant association materialised from regression modelling. This result suggests that a lack of geographic access does not increase the risk of being diagnosed later with more severe symptoms.

This result has potentially further meaning. For if individuals with further to travel to primary healthcare are at no greater risk of liver-related mortality and, by proxy, no more likely to be diagnosed at a later stage of infection, this also suggests that persons with further to travel to consult their GP are no less likely to be diagnosed. Thus, the results of this chapter are in broad agreement with the conclusion to an earlier chapter, that detection rates of HCV are not lower amongst population groups lacking geographic access to primary healthcare.

In fact, however, it appeared that living closer to the HCV specialist centre increased the risk of death from all-causes and drugs-related causes. Although at first counterintuitive, it is probably the case that these trends occurred due to an insufficient adjustment for mortality risks associated with less-favourable socioeconomic position (Boyle, Exeter, and Flowerdew 2004; Davey Smith, Blane, and Bartley 1994), of which the ecological-based Carstairs deprivation score may not fully control for.

The principal finding of this chapter, however, could be viewed as the very strong association between non-referral and all categories of death that were modelled. This raises questions that the data here is unable to really answer. For instance, were patients not referred because of the severity of the symptoms presented at diagnosis,

which subsequently rendered the potential for HCV treatment success very low and the risk of death high? Were patients with poor geographic access to healthcare less likely to be referred because of the severity at which HCV was diagnosed? Although death from liver-related causes is a good indicator that something was wrong and the results here suggest it is unlikely, death is no more than a crude proxy and a more direct measure of severity would be preferable had there been one available. Perhaps the most realistic hypothesis is that many patients were diagnosed in hospital as a result of delayed health-seeking behaviour. Thus, bypassing their GP when symptoms became too severe to ignore, by which time the more appropriate treatment would be a liver transplant. Unfortunately, the data did not include information on precisely where and by whom each patient was diagnosed, but this information would have been useful to tease out plausibility to this and other hypotheses.

There are other weaknesses to this study, notably the small numbers of deaths from liver-related causes. A larger sample would have been preferable for providing more robust estimates and also provided the opportunity to distinguish between mortality shortly after detection from that later on, as a further proxy for more advanced symptoms at diagnosis. However, no larger samples with sufficiently detailed variables (particularly on residential geography) were available to analyse.

Mortality from liver-related causes is rising in the UK, especially in Scotland (Bosetti et al. 2007; La Vecchia et al. 2000; Leon and McCambridge 2006; Leyland, Dundas, McLoone,

and Boddy 2007). HCV is already a leading cause of liver cancer and cirrhosis worldwide (Giacosa and Hill 1996; Ince and Wands 1999; Perz and Alter 2006; Perz et al. 2006) and the low HCV detection rates in Scotland mean that if patients are not being diagnosed early, there will be a lot of people with advanced liver disease that requires transplants, not HCV combination therapy. Exploring all factors that might be influencing the lack of detection is therefore important, but this should not be to the detriment of reporting how those who have been diagnosed fare with getting access to specialist healthcare. Low rates of referral are a worry, and these results suggest that the real cost of the health service may lie, not with the small number of patients who are referred unnecessarily or inappropriately, but with those patients who are referred late or not at all (Marinker, Wilkin, and Metcalfe 1988; Wilkin, Metcalfe, and Marinker 1989).

## **8.8 Summary**

### **8.8.1 What we knew before?**

Low rates of detection and referral to specialist centres for individuals infected with HCV are recognised, but little is known about what is causing them. Patients lacking geographic access to healthcare might be diagnosed later into the course of infection



when symptoms are more severe, possibly reducing the likelihood that they will be referred, but no study has so far explored the extent to which this might be occurring.

### **8.8.2 What this study has contributed?**

The results of this study demonstrate that the risk of death from liver-related causes is not higher amongst persons with further to travel to seek healthcare, primary or specialist. Thus, a lack of geographic access does not appear to be associated with more severe liver disease as a result of delayed presentation.

Furthermore, patients that were not referred to an HCV specialist centre were at an elevated risk of death from all causes, liver-related and drugs-related.

### **8.8.3 What gaps remain?**

The possibility that patients are not diagnosed by a GP, but by a hospital as a result of delayed health-seeking behaviour is a possibility not yet explored in the context of HCV. This may be a reason why so many patients that died were unreferral, as the severity of their condition might have precluded HCV treatment.

In addition, the study presented in this chapter requires replication with larger study samples and better measures of disease severity.

# **9. Are chances of survival from HCV infection associated with the type of diagnosing location?**

## **9.1 Introduction**

In the previous chapter, it was hypothesised that a lack of geographic access to healthcare, primary or specialist, would exacerbate delays in health-seeking behaviour and increase the likelihood of liver-related causes of death amongst individuals diagnosed with HCV. The results showed neither travel-time to primary healthcare, nor to an HCV specialist centre were found to significantly associate with the risk of liver-related mortality in patients diagnosed with HCV in NHS Tayside. Drugs-related mortality was greater amongst those living in closer proximity to the specialist centre, which is probably an artefact of higher IDU prevalence in more deprived inner city locations (Craine, Walker, Carnwath, and Klee 2004; Hutchinson et al. 2004) where Ninewells Hospital is located and an insufficient adjustment for IDU risk factors in the models.

However, curiously, non-referral to the specialist centre strongly predicted mortality for each cause of death analysed and referral was shown in another previous chapter to be less likely amongst patients with furthest to travel to an HCV specialist centre. This raised several questions, the most notable being whether the lack of referral amongst deceased patients was due to diagnosis taking place in secondary, rather than primary, healthcare locations? This is a significant possibility, as health-seeking behaviour more commonly occurs after the onset of symptoms and delays can have deleterious consequences for prognosis (Afzelius, Zedeler, Sommer, Mouridsen, and Blichert-Toft 1994; Arndt, Stürmer, Stegmaier, Ziegler, Dhom, and Brenner 2002; Jensen, Nellesmann, and Overgaard 2007; Korsgaard, Pedersen, Sørensen, and Laurberg 2006; Richards, Smith, Ramirez, Fentiman, and Rubens 1999; Richards, Westcombe, Love, Littlejohns, and Ramirez 1999) that may necessitate the attention of the nearest hospital, not the nearest GP. The severity of the HCV-related complications uncovered at diagnosis may have required more radical treatment (e.g. a liver transplant) or been limited only to palliative care.

So far, no study in Scotland has explored variation in liver-related causes of death amongst a population infected with HCV according to the type of healthcare location at which diagnosis took place. It is hypothesised that a selection effect is possible, with patients delaying seeking healthcare more likely to present in hospitals whereas those diagnosed in primary healthcare may be a more health-seeking population or detected early due to risk group-targeted screening programmes.

In addition, as awareness of HCV is known to vary considerably within the medical profession (d'Souza et al. 2004), it may be that patients diagnosed in hospitals where there is an HCV specialist centre on site may benefit from that hub of expertise and have better outcomes compared to those diagnosed in other hospitals. Assuming patients will attend their nearest hospital if their health condition dictates bypassing a visit to the GP, it may be that patients with less access to an HCV specialist centre fare poorer outcomes overall.

Hence, this chapter aimed to explore two questions:

- 1 To what extent is the likelihood of death from liver-related causes greater amongst patients diagnosed with HCV in secondary than primary healthcare locations?
- 2 Is there a protective effect of being diagnosed in a secondary healthcare location with a HCV specialist centre on site?

## **9.2 Methodological approach**

In this chapter, like the previous chapter that explored whether geographic access was associated with cause-specific mortality, the response variables for the forthcoming analyses are also dichotomous and a Cox regression model employed. Hazard ratios

above 1 indicate positive association between the explanatory variable and the risk of mortality, whereas below 1 suggests negative association. Standard errors and p-values are given sensu previous chapters.

## **9.3 Study specification**

### **9.3.1 Study sample and setting**

The datasets used throughout previous chapters lacked information on precisely where and in what type of healthcare location each patient was diagnosed. For the following analyses, the HCV diagnosis database maintained by Health Protection Scotland (HPS) was utilised as it contained such variables. Similar to ELDIT, this is a database that contains HCV anti-body positive diagnoses since 1991 (Shaw et al. 2003). But unlike ELDIT, this database is national, and so contains a much larger sample size consisting of all individuals diagnosed in Scotland 1991-2006.

Patients were defined by existing variables within the diagnoses database by age at the time of HCV detection, sex, disclosed history of IDU, date and cause of death where relevant. Each of the 22,073 patients diagnosed up to 31<sup>st</sup> December 2006 had been categorised by HPS according to the type of healthcare location at which diagnosis was

made. These included (#; %): i) hospitals (9234; 42%); ii) GPs (4616; 21%); iii) genitourinary (GUM) clinics (1133; 5%); iv) prisons (1343; 6%); or v) other/unknown location types. Patients detected in prisons were excluded from the dataset for the same reasons as in prior chapters. Patients for whom nothing was known of the type of healthcare diagnosed in, or the type was unclassifiable or 'other', were also omitted on the grounds of inconsistency. Omitting patients in this way may have introduced bias in the sample, but the focus was strictly on the potential differential between being diagnosed in a primary versus a hospital setting. All patients classified with location types as hospitals, GP practices or GUM clinics were kept in the dataset. Any other patients without information on other explanatory variables were also omitted. A total number of 7744 patients were omitted from the dataset, leaving 14,329 to analyse with full data availability.

### **9.3.2 Variable definition**

The Scottish death register was linked by HPS to the HCV diagnoses database to provide information on the causes of death where relevant, classified to the International Classification of Diseases (ICD) 9<sup>th</sup> and 10<sup>th</sup> revisions, corresponding to years 1980-1999 and 2000-2005 respectively. ICD-9 codes were mapped to the ICD-10 classification using a published look-up table (New Zealand Ministry of Health Information Service

2008) to facilitate a further classification of causes according to the typology used by Amin and colleagues (Amin et al. 2006). This involved identifying 'liver-related' causes of death, including: i) alcoholic liver disease (K70); ii) liver cancer (C22); iii) non-alcoholic liver disease (K71-K77); iv) sequale of viral hepatitis (B9462); and v) viral hepatitis (B15-B19). A second type, 'drugs-related' causes of death were also identified for comparison, including codes: F1-F16; F19; F55; X40-X44; X60-X64; X85; Y10-Y14.

To explore variation in each cause of death according to healthcare location type, patients diagnosed in GP practices and GUM clinics were aggregated to represent primary healthcare. Patients diagnosed in hospitals were disaggregated according to whether the hospital they were diagnosed in contained an HCV specialist centre on site. These hospitals were identified through personal communication with Dr Dillon (Consultant Hepatologist and Gastroenterologist, NHS Tayside) and Dr Hutchinson (Senior Epidemiologist, Health Protection Scotland) and are listed below and mapped (Figure 14.1):



## HCV Specialist Centres

1. Raigmore Hospital (RH)
2. Aberdeen Royal Infirmary (ABR)
3. Ninewells Hospital (NH)
4. Stirling Royal Infirmary (SRI)
5. Royal Infirmary of Edinburgh (RIE)
6. Western General Hospital (WGH)
7. Glasgow Royal Infirmary (GRI)
8. Southern General Hospital (SGH)
9. Brownlee Centre Glasgow (GGH/BCG)
10. Gartnavel General Hospital (GGH/BCG)
11. Dumfries and Galloway Royal Infirmary (D&G)
12. Inverclyde Royal Hospital (IRH)
13. Monklands Hospital (MH)
14. Crosshouse Hospital (CRH)
15. Borders General Hospital (BGH)
16. Victoria Hospital (VH)
17. Cameron Hospital (CMH)

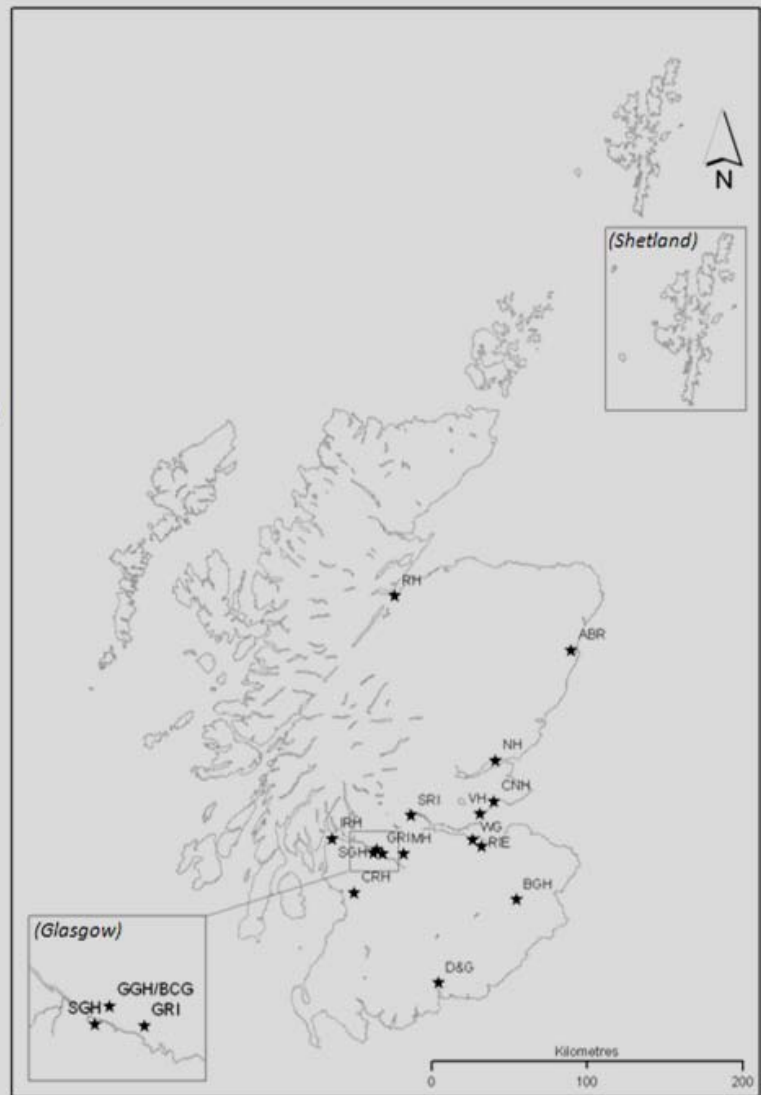


Figure 14.1: Map of HCV specialist centres in Scotland (key left)

For other geographical identifiers, unfortunately, the dataset was very limited with only a very coarse scale of residential data stored (the postcode district), which would not have been a reliable approach to measuring the utilisation of healthcare locations by travel-time or any other measure of geographic accessibility. For the same reason, the following analyses have not been adjusted for socioeconomic position using an ecological measure of socioeconomic deprivation, nor standard individual measures (e.g.

occupationally-defined social class). The IDU measure will have adjusted for this heterogeneity at least partially, because of the correlation between drug misuse and deprivation.

### **9.3.3 Analysis specification**

Associations between liver-related and drugs-related cause mortality and each explanatory variable were explored with multivariate Cox regression models per response, as explained in the previous chapter. To control for the competing risks of death from liver-related, drugs-related or any other cause, individuals that died because of a cause that was not the response variable of interest were omitted (i.e. in models of liver-related mortality, patients that died from non-liver-related causes were not analysed). Indirect comparisons of the direction and statistical significance of associations were made across models.

Again, the data lacked information on the severity of HCV progression at diagnosis. However, as the data were in larger numbers, discrete survival time periods were calculated to serve as proxy. Patients dying within 12 months of being diagnosed due to liver-related causes were identified as most likely to be presenting with a more severe stage of HCV progression, contrasting those dying of similar causes but within a 1-10 year time period with milder symptoms and a greater window of opportunity for

intervention. Drugs-related deaths were categorised in a similar way for consistency when comparing associations.

Since the data was nested (patients into healthcare locations), robust standard errors with a cluster option was utilised to allow for spatial clustering (UCLA: Academic Technology Services 2008; Williams 2000). This technique has been used in several recently published thesiss, where like the objective of this chapter, the variation between each individual location was not the main focal point of considerable interest (Gayle, Boyle, Flowerdew, and Cullis 2008; Mitchell and Popham 2008; Thomas, Benzeval, and Stansfeld 2005; Van Ham and Manley 2009).

## 9.4 Descriptives

Cause of death (ICD-10 code)	x <1 year		10 years => x >1 year	
	#	%	#	%
Liver-related	174	32.6	235	24.2
<div style="display: flex; align-items: center;"> <div style="margin-right: 10px;">Liver-related causes by category</div> <div style="margin-right: 10px;">{</div> <ul style="list-style-type: none"> <li>Alcoholic liver disease (K70)</li> <li>Liver cancer (C22)</li> <li>Non-alcoholic liver disease (K71-K77)</li> <li>Sequale of viral hepatitis (B9462)</li> <li>Viral hepatitis (B15-B19)</li> </ul> </div>	66	12.4	115	11.8
	34	6.4	38	3.9
	34	6.4	27	2.8
	4	0.8	4	0.4
	36	6.8	51	5.3
Drugs-related (F1-F16; F19; F55; X40-X44; X60-X64; X85; Y10-Y14)	132	24.8	274	28.2
Not drugs or liver-related	227	42.6	462	47.6
Total number of deaths		533		971
Total patients surviving		13796		12825
Total patients		14329		13796

**Table 14.1: Classified causes of death, by time of death**

A total of 22,073 anti-body positive HCV infections were detected in Scotland up to 31<sup>st</sup> December 2006. 14,329 patients were selected, having been detected in primary or secondary healthcare settings with full unit postcode georeferencing. 1503 patients died within 10 years of detection, 533 within the first year and 971 in the following 9. Table 14.1 reports how these deaths were distributed, grouped into liver-related, drugs-related and other causes. Liver-related causes of death within the first year, at 32.6%, were more common than drugs-related causes (24.8%). In contrast, liver-related causes were slightly less common than drugs-related causes in patients surviving between 1 and 10 years after diagnosis (24.2% to 28.2%). Liver-related causes of death were mainly attributable to alcoholic liver disease in both time periods (12.4% < 1year, 11.8% > 1 year). Liver cancer (6.4%), non-alcoholic liver disease (6.4%) and viral hepatitis (6.8%) were more common causes of death within a year of diagnosis than in the following 9 years.

Table 14.2 describes the characteristics of those individuals that died within each time period, for liver-related and drugs-related causes only. Men outnumbered women in both time periods, consistently above 70% for both causes of death. The greatest variation was for deaths within 1 year of diagnosis, with men amongst 70.1% of liver-related and 76.5% of drugs-related causes of death. The mean age at diagnosis tended to be higher amongst individuals suffering liver-related deaths in both time periods (< 1 year: 54.4; > 1 year: 44.8) compared with those suffering drugs-related causes (~31 in both time periods). These trends are reassuring given that the likelihood of developing

liver-related complications from HCV tended to occur decades after the initial infection, whereas IDU is more prevalent amongst younger individuals.

Characteristic	x <1 year				10 years => x >1 year			
	Liver-related		Drugs-related		Liver-related		Drugs-related	
Sex (#, %)								
<i>Women</i>	52	29.9	31	23.5	59	25.1	70	25.5
<i>Men</i>	122	70.1	101	76.5	176	74.9	204	74.5
Mean age (min - max)	54.4	(22-89)	31.5	(17-54)	44.8	(20-87)	31.0	(17-54)
History of intravenous drug use (#, %)								
<i>Injected</i>	31	17.8	104	78.8	91	38.7	220	80.3
<i>Never injected</i>	143	82.2	28	21.2	144	61.3	54	19.7
Location type (#, %):								
<i>Specialist</i>	76	43.7	48	36.4	98	41.7	96	35.0
<i>Primary</i>	11	6.3	39	29.5	43	18.3	97	35.4
<i>Hospital</i>	87	50.0	45	34.1	94	40.0	81	29.6
Mean months survival (min-max)	3.9	(0-12)	4.6	(0-12)	48.8	(13-114)	45.6	(13-116)

**Table 14.2: Causes of death related to viral hepatitis C diagnosed in primary and secondary healthcare, by time of death**

Similar assurances are found with the history of IDU indicator, with high percentages of drugs-related deaths among those with a history of injecting (< 1 year: 78.8%; > 1 year: 80.3%). By comparison, the majority of liver-related causes of death within 1 year did not disclose a history of IDU (82.2%), but less of a clear majority amongst deaths between 1 and 10 years (61.3%). In terms of the type of location, patients diagnosed by a GP were in the minority for deaths from liver-related causes (6.3%), with far more diagnosed in a hospital (43.7%) with an HCV specialist centre on site and 50% in all other hospitals. Figure 14.2 aids interpretation of this inequality, which is also observed but less extreme amongst liver-related causes of death between 1 to 10 years. Drugs-related deaths seemed to be far more evenly spaced out across each location type by

contrast. Mean survival for both causes of death within 1 year was approximately 4 months, with also similar survival times in the period 1-10 years (liver: 48.8; drugs: 45.6).

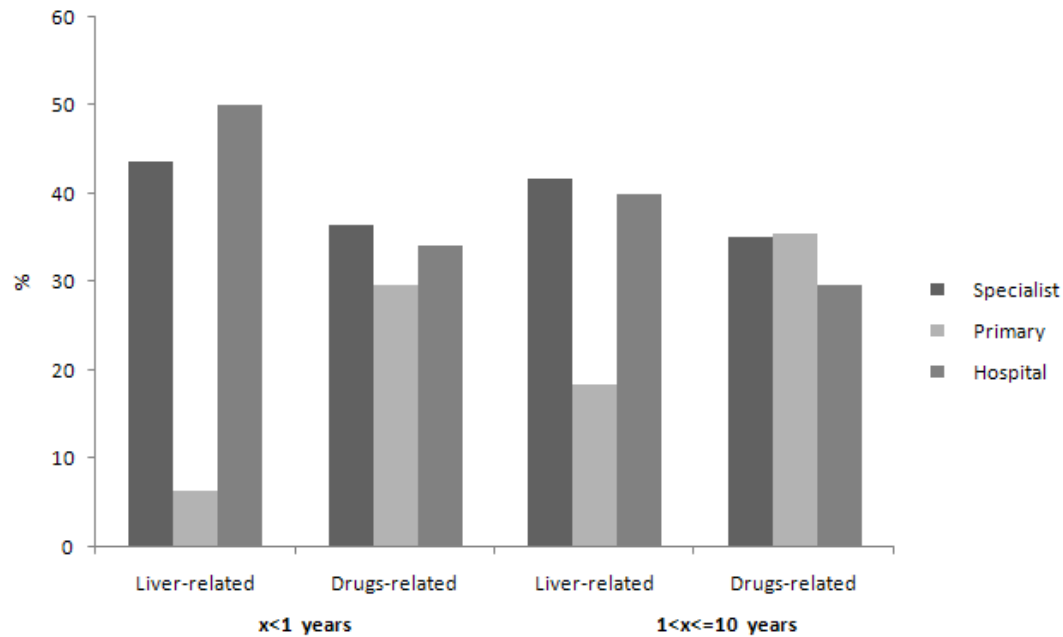


Figure 14.2: Percentage share of deaths among patients with HCV, by cause of death, time period and diagnosis location type

## 9.5 Multivariate associations: variation between location type

Multivariate Cox regression models for the four response variables were used to explore the trends identified in the descriptives. Different response variables were modelled with explanatory variables added sequentially. The results are illustrated in separate tables. Hazard ratios above 1 indicate positive association between response and the explanatory, whereas ratios below 1 imply negative association. In Model 1, essentially

a univariate model fitting the risk of death from liver-related causes and the men/women differential, the hazard ratio of 1.451 (p-value: 0.041) suggests that men were at greater risk of death than women, though the association had weak statistical significance. However, with the addition of the age variable in Model 2, itself positively associated with death (hazard ratio: 1.096, p-value: <0.001) as expected, the hazard ratio for men compared with women increases to 1.468 (p-value: 0.025), suggesting that older men are at greater risk.

	Model 1			Model 2			Model 3			Model 4		
	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value
<i>Sex (base: women)</i>												
Men	1.451	0.265	0.041	1.468	0.251	0.025	1.564	0.265	0.008	1.499	0.258	0.019
<i>Age</i>												
				1.096	0.006	<0.001	1.084	0.006	<0.001	1.080	0.006	<0.001
<i>IDU history (base: never injected)</i>												
Injected							0.345	0.101	<0.001	0.415	0.123	0.003
<i>Location type (base: HCV specialist centre)</i>												
Hospital										1.576	0.375	0.056
Primary										0.240	0.085	<0.001
N (patients)	13168			13168			13168			13168		
# clusters	675			675			675			675		
# deaths analysed	145			145			145			145		
Times at risk	1047898			1047898			1047898			1047898.000		
log pseudolikelihood	-1372.556			-1204.371			-1193.906			-1169.456		
Wald chi2	4.160			293.380			296.330			378.540		
Prob > chi2	0.041			<0.001			<0.001			<0.001		

**Table 14.3: Multivariate associations between survival and explanatory variables (variation between location types): Cox proportional hazard models (liver-related 1 year mortality)**

Adding the history of IDU differential further increases the magnitude and statistical significance of the hazard ratio for men (hazard ratio: 1.564, p-value: 0.008). Individuals with a history of IDU, however, were strongly less likely to die of liver-related causes than those with no injecting history (hazard ratio: 0.345, p-value: <0.001). Finally, the main explanatory test variable of diagnosing location type was added to the model (4),

itself a three-fold categorical variable with hospitals containing an HCV specialist centre set as the baseline from which other Hospitals and Primary healthcare were allowed to vary. Strong hazard ratios operating in opposite directions were observed, with the likelihood of liver-related death higher amongst those diagnosed in a hospital without a specialist HCV centre (hazard ratio: 1.576, p-value: 0.056), though marginally insignificant, but significantly lower for individuals diagnosed in primary healthcare (GP or GUM clinic) (hazard ratio: 0.240, p-value: <0.001).

Importantly, these results suggest that death from liver-related causes within a year of being diagnosed with HCV, reflecting late-stage presentation of symptoms at detection, are more common in secondary healthcare locations. The presence of an HCV specialist centre maybe providing a protective effect for some hospitals, whilst the low risk of liver-related death for patients diagnosed by a GP implies a selection effect, whereby patients that delay health-seeking behaviour are more likely to be diagnosed in a hospital.

	Model 5			Model 6			Model 7			Model 8		
	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value
Sex (base: women)												
Men	1.738	0.263	<0.001	1.698	0.259	0.001	1.746	0.268	<0.001	1.756	0.280	<0.001
Age												
				1.070	0.006	<0.001	1.065	0.007	<0.001	1.063	0.007	<0.001
IDU history (base: never injected)												
Injected							0.712	0.127	0.056	0.817	0.138	0.231
Location type (base: HCV specialist centre)												
Hospital										1.067	0.285	0.809
Primary										0.422	0.110	0.001
N (patients)												
	13023			13023			13023			13023		
# clusters												
	674			674			674			674		
# deaths analysed												
	235			235			235			235		
Times at risk												
	1047225			1047225			1047225			1047225		
log pseudolikelihood												
	-2129.503			-2015.656			-2013.185			-1997.259		
Wald chi2												
	13.360			186.060			208.370			240.450		
Prob > chi2												
	<0.001			<0.001			<0.001			<0.001		

**Table 14.4: Multivariate associations between survival and explanatory variables (variation between location types): Cox proportional hazard models (liver-related 10 year mortality)**



For comparatively more long-term survival but the likelihood of death from liver-related causes (Table 14.4), Model 5 again univariately finds men to be at significantly greater risk than women (hazard ratio: 1.738, p-value: <0.001). Unlike deaths within 1 year of diagnosis, adding age into the model (6), itself positively associated with the risk of death as expected (hazard ratio: 1.070, p-value: <0.001), also attenuates the association with men (hazard ratio: 1.698, p-value: <0.001). As before, the risk of liver-related death is less likely amongst those individuals with a history of IDU (Model 7), though marginally insignificant (hazard ratio: 0.712, p-value: 0.056).

However, adding the location type of healthcare at which an individual was diagnosed reveals no statistical difference in the risk of liver-related death between hospitals with and without an HCV specialist centre on site. Whereas those diagnosed in primary healthcare continued to be at lower risk (hazard ratio: 0.422, p-value: 0.001) again pointing towards selection of those at greatest risk into secondary healthcare.

Table 14.5 illustrates models for drugs-related deaths within 1 year of diagnosis. In Model 9, men were more likely than women to die of drugs-related causes (hazard ratio: 1.651, p-value: 0.015) and this association increased in magnitude and significance (hazard ratio: 1.714, p-value: 0.009) in Model 10 with the addition of age, for whom younger individuals were at greater risk (hazard ratio: 0.979, p-value: 0.033).

The age association, however, was rendered statistically insignificant with the introduction of the positively associated IDU history differential (hazard ratio: 1.752, p-

value: 0.004) in Model 11, which also attenuated the association with men in both magnitude and significance (hazard ratio: 1.654, p-value: 0.016). Adding in location type for Model 12 displayed no statistically significant results, though the direction of effect was similar to that previously observed for liver-related causes of death with one year of diagnosis.

	Model 9			Model 10			Model 11			Model 12		
	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value
<i>Sex (base: women)</i>												
Men	1.651	0.339	0.015	1.714	0.354	0.009	1.654	0.345	0.016	1.687	0.356	0.013
<i>Age</i>												
				0.979	0.010	0.033	0.986	0.010	0.168	0.986	0.010	0.181
<i>IDU history (base: never injected)</i>												
Injected							1.752	0.342	0.004	1.830	0.368	0.003
<i>Location type (base: HCV specialist centre)</i>												
Hospital										1.063	0.318	0.838
Primary										0.782	0.205	0.348
N (patients)	13161			13161			13161			13161		
# clusters	677			677			677			677		
# deaths analysed	105			105			105			105		
Times at risk	1048044			1048044			1048044			1048044		
log pseudolikelihood	-992.833			-990.785			-987.743			-986.810		
Wald chi2	5.960			10.820			18.790			20.010		
Prob > chi2	0.015			0.005			0.000			0.001		

**Table 14.5: Multivariate associations between survival and explanatory variables (variation between location types): Cox proportional hazard models (drugs-related 1 year mortality)**

Table 14.6 shows model results for drugs-related causes of death between 1 and 10 years of an HCV diagnosis. In Model 13, men were again at significantly greater risk (hazard ratio: 1.703, p-value: <0.001) and the strength of this association was increased (hazard ratio: 1.752, p-value: <0.001) by the addition of age into Model 2. Again, patients diagnosed at a younger age were at significantly greater risk of drugs-related death during this time period (hazard ratio: 0.980, p-value: <0.001) and continued to be, albeit the association of which was attenuated by the addition of IDU history, which as

before, was also positively associated with the risk of drugs-related death (hazard ratio: 2.138, p-value: <0.001).

Adding the location type where diagnosed into the model demonstrated the negative association between those detected in primary healthcare relative to hospitals with an HCV specialist centre on site previously reported in all other models (hazard ratio: 0.684, p-value: 0.019). However, in departure, patients diagnosed in hospitals without a specialist centre were also less likely to die of drugs-related causes though this association was not statistically significant (hazard ratio: 0.930, p-value: 0.652).

	Model 13			Model 14			Model 15			Model 16		
	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value
<i>Sex (base: women)</i>												
Men	1.703	0.235	<0.001	1.753	0.243	<0.001	1.671	0.231	<0.001	1.713	0.239	<0.001
<i>Age</i>												
				0.980	0.005	<0.001	0.990	0.005	0.042	0.990	0.005	0.051
<i>IDU history (base: never injected)</i>												
Injected							2.138	0.370	<0.001	2.277	0.394	<0.001
<i>Location type (base: HCV specialist centre)</i>												
<i>Hospital</i>												
Primary										0.930	0.150	0.652
										0.684	0.111	0.019
N (patients)	13056			13056			13056			13056		
# clusters	676			676			676			676		
# deaths analysed	274			274			274			274		
Times at risk	1047435			1047435			1047435			1047435		
log pseudolikelihood	-2495.706			-2491.166			-2477.870			-2473.996		
Wald chi2	14.890			27.830			41.290			47.450		
Prob > chi2	<0.001			<0.001			<0.001			<0.001		

**Table 14.6: Multivariate associations between survival and explanatory variables (variation between location types): Cox proportional hazard models (drugs-related 10 year mortality)**

## 9.6 Multivariate associations: variation within location type

The next stage of analyses explored variation within the types of diagnosing locations. Models for each response and time period are illustrated along-side each other for indirect comparisons, with all explanatory variables fitted simultaneously. For patients diagnosed in hospitals with an HCV specialist centre or in primary healthcare locations, men were not at significantly greater risk of a liver-related cause of death within 1 year of diagnosis. Men were, however, at greater risk when diagnosed in hospitals without a specialist unit (hazard ratio: 2.038, p-value: 0.014). Patients detected in older age were at significantly greater risk of liver-related death irrespective of where they were diagnosed (Table 14.7), whereas a history of IDU was only negatively associated with mortality risk amongst those diagnosed in hospitals without an HCV specialist centre (hazard ratio: 1.1962, p-value: 0.018).

	Model 13 (Specialist)			Model 14 (Primary)			Model 15 (Hospital)		
	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value
<i>Sex (base: women)</i>									
Men	1.160	0.255	0.499	1.084	0.578	0.879	2.038	0.591	0.014
Age	1.076	0.008	<0.001	1.099	0.019	<0.001	1.079	0.010	<0.001
<i>IDU history (base: never injected)</i>									
Injected	0.740	0.235	0.343	0.460	0.374	0.339	0.196	0.135	0.018
N (patients)	4619			5141			3408		
# clusters	25			549			101		
# deaths analysed	61			11			73		
Times at risk	331119			407959			308820		
log pseudolikelihood	-466.394			-79.819			-486.836		
Wald chi2	161.250			122.340			163.680		
Prob > chi2	<0.001			<0.001			<0.001		

**Table 14.7: Multivariate associations between survival and explanatory variables (variation within location types): Cox proportional hazard models (liver-related 1 year mortality)**

	Model 16 (Specialist)			Model 17 (Primary)			Model 18 (Hospital)		
	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value
<i>Sex (base: women)</i>									
Men	2.066	0.378	<0.001	1.169	0.365	0.618	1.755	0.526	0.061
<i>Age</i>									
	1.055	0.011	<0.001	1.095	0.011	<0.001	1.063	0.009	<0.001
<i>IDU history (base: never injected)</i>									
Injected	0.584	0.121	0.009	1.844	0.748	0.132	0.857	0.244	0.589
N (patients)	4558			5130			3335		
# clusters	25			548			101		
# deaths analysed	98			43			94		
Times at risk	330855			407877			308493		
log pseudolikelihood	-731.921			-327.972			-687.164		
Wald chi2	75.040			109.790			107.150		
Prob > chi2	<0.001			<0.001			<0.001		

**Table 14.8: Multivariate associations between survival and explanatory variables (variation within location types): Cox proportional hazard models (liver-related 10 year mortality)**

In contrast, for liver-related causes of death between 1 and 10 years following diagnosis (Table 14.8), only men (relative to women) diagnosed in a hospital with a specialist centre were at significantly greater risk (hazard ratio: 2.066, p-value: <0.001). Though positive associations were also observed for the other locations, neither was statistically significant to the 0.05 level. Patients diagnosed in older age were at significantly greater risk of death irrespective of where diagnosed, though a history of IDU was only negatively associated with patients diagnosed in hospitals with an HCV specialist centre onsite.

Tables 14.9 display the modelling results of variation within location types for drugs-related causes of death within 1 year. Men were only significantly at greater risk of death compared to women when diagnosed in a hospital without an HCV specialist centre (Table 14.9), albeit with weak statistical significance (hazard ratio: 2.758, p-value:

0.044). The directions of effect suggested that younger patients diagnosed in secondary healthcare were at greater risk of a drugs-related death, though only hospitals without specialist centres were close to statistical significance (hazard ratio: 0.971, p-value: <0.061). Although hazard ratios above 1 were reported for patients with a history of IDU in each location type, only those diagnosed in hospitals with an HCV specialist centre were statistically significant within the 0.05 level (hazard ratio: 1.655, p-value: 0.044).

	Model 19 (Specialist)			Model 20 (Primary)			Model 21 (Hospital)		
	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value
<i>Sex (base: women)</i>									
Men	1.569	0.470	0.133	1.263	0.444	0.507	2.758	1.390	0.044
Age	0.982	0.018	0.301	1.002	0.019	0.905	0.971	0.015	0.061
<i>IDU history (base: never injected)</i>									
Injected	1.655	0.414	0.044	2.081	0.945	0.106	1.862	0.757	0.126
N (patients)	4587			5224			3350		
# clusters	25			551			101		
# deaths analysed	37			38			30		
Times at risk	329662			411188			307194		
log pseudolikelihood	-309.036			-323.336			-238.207		
Wald chi2	5.680			4.040			26.230		
Prob > chi2	0.128			0.258			<0.001		

**Table 14.9: Multivariate associations between survival and explanatory variables (variation within location types): Cox proportional hazard models (drugs-related 1 year mortality)**

	Model 22 (Specialist)			Model 23 (Primary)			Model 24 (Hospital)		
	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value	Hazard Ratio	Standard Error	p-value
<i>Sex (base: women)</i>									
Men	2.959	0.672	<0.001	1.396	0.333	0.162	1.273	0.244	0.208
Age	0.990	0.006	0.119	0.999	0.011	0.917	0.982	0.008	0.019
<i>IDU history (base: never injected)</i>									
Injected	2.179	0.577	0.003	2.262	0.760	0.015	2.421	0.731	0.003
N (patients)	4550			5186			3320		
# clusters	25			550			101		
# deaths analysed	96			97			81		
Times at risk	329461			410938			307036		
log pseudolikelihood	-752.740			-785.724			-630.404		
Wald chi2	25.480			11.310			13.070		
Prob > chi2	<0.001			0.010			0.005		

**Table 14.10: Multivariate associations between survival and explanatory variables (variation within location types): Cox proportional hazard models (drugs-related 10 year mortality)**

Table 14.10 displays hazard ratios for drugs-related deaths between 1 and 10 years of diagnosis. Hazard ratios above 1 for the men/women differential amongst patients diagnosed in each type of location suggested that men were at greater risk of a drugs-related death than women, though statistical significance was only achieved for those diagnosed in hospitals with an HCV specialist centre (hazard ratio: 2.959, p-value: <0.001). Similarly, ratios below 1 for age in each location type pointed towards greater risk of drugs-related deaths amongst patients diagnosed at younger ages, though the only significant association this time was for those diagnosed in hospitals without a specialist centre (hazard ratio: 0.982, p-value: 0.019). Unsurprisingly, patients suffering a drugs-related death were significantly more likely to have a history of IDU, with strong magnitude and significant hazard ratios for each location type.

## **9.7 Discussion**

This chapter set out to explore whether the type of healthcare provider at which an individual infected with HCV receives diagnosis was associated with an increased risk in cause-specific mortality. HCV diagnosed at an early stage of progression should enable the possibility for treatment at an HCV specialist centre and improved chances of clearing the virus. In persons with a history of IDU, targeted for HCV screening as the major risk group in Scotland, early diagnosis is quite possible. Other individuals that

were infected by blood transfusion, a previous experience of IDU that never became a habit, or by another mode of transmission not explicitly targeted for screening are likely to be detected once symptoms of HCV-related liver diseases emerge. By which time, perhaps, it may be more likely for patients to be admitted direct to the nearest hospital instead of the local GP practice. Hence, for patients detected in hospital locations, it was hypothesised that the risk of liver-related causes of death to be much greater than for those diagnosed in primary healthcare.

Findings from this chapter were supportive, since mortality from liver-related causes did appear to vary between the type of healthcare in which patients were diagnosed. Compared to those patients diagnosed in hospitals, patients diagnosed by GPs were less likely to die of liver-related causes. This was the case in both time periods, but especially for deaths within 1 year of diagnosis which were taken as a proxy for being diagnosed at a late stage of HCV symptoms progression. In contrast, deaths due to drugs-related causes were more evenly distributed between healthcare location types and tended to occur amongst younger patients with a history of IDU, whereas the obverse was evident for deaths from liver-related causes.

Interesting variation was also noted between hospitals with an HCV specialist centre on site and those that did not. HCV specialist centres were hypothesised to have a knowledge-spillover effect in so that patients diagnosed in these hospitals would have more favourable chances of survival than those in other hospitals without a specialist on



site. Patients diagnosed in hospitals without a specialist were at greater risk of death from liver-related causes within a year of detection compared with those patients diagnosed in hospitals with a specialist centre (though the association was marginally insignificant).

It is highly likely that there is a selection effect involving healthcare-seeking behaviour. Men, for instance, are well known to be more reluctant to consult GPs on potentially cancer-related issues (Antonovsky and Hartman 1974; Risberg, Sorbye, Norum, and Wist 1996; Young, Sweeney, and Hunter 2000). The results here demonstrated that men were at greater risk of a liver-related death within 1 year and between 1 and 10 years of diagnosis. Men were also more likely to die of liver-related causes if diagnosed in hospital settings, whereas there was no significant difference between men and women diagnosed by a GP. Furthermore, whilst it is no surprise that patients diagnosed at an older age were at greater risk of liver-related complications, poorer levels of mobility amongst some older persons should also be appreciated as a potential cause of delayed health-seeking behaviour.

Other selection effects could not be controlled for unfortunately. Socioeconomic position is the most important omission and research has shown in other contexts that individuals from less favourable positions are more likely to normalise symptoms (Bain and Campbell 2000; Corner, Hopkinson, and Roffe 2006) and delay healthcare-seeking behaviour (Gardner, Chapple, and Green 1999; Richards, Reid, and Watt 2002; Tod,

Read, Lacey, and Abbott 2001). Whilst a history of IDU is associated with socioeconomic deprivation, there will be many individuals not disclosing a history of IDU that do occupy less favourable socioeconomic positions. Furthermore, as this indicator is a binary, it is not clear whether persons that had tried IDU in the past once or twice without it ever becoming a habit were likely to indicate a history of injecting or not. Finally, the absence of any small-scale residential data meant that the measurement of geographic accessibility and utilisation patterns were not possible.

However, there are significant merits to the analyses presented in this chapter. It has identified that actually a large number of patients are detected in hospitals, rather than primary healthcare settings, and that liver-related mortality is more likely amongst patients diagnosed in the former than the latter. It may be, therefore, that a partial explanation for the low rates of referral to specialist centres occurs because patients are being diagnosed at a late stage of progression in hospital settings. Moreover, the presence of an HCV specialist centre in a hospital might be beneficial for raising the chances of survival amongst patients, possibly through earlier detection of patients or spreading awareness amongst fellow medical staff. Future research might want to consider whether the presence of a specialist centre is associated with increased awareness amongst hospital staff and GPs in the local vicinity.

Further research is also needed to explore how levels of geographic access and availability of healthcare and socioeconomic position influence health-seeking

behaviour amongst persons infected with HCV. If effective strategies aimed at tackling the coming wave of HCV-related liver disease are to be successful, studies that explore geographic trends and are able to identify populations particularly at risk of late detection will be important.

## **9.8 Summary**

### **9.8.1 What we knew before?**

Patients that do not fit the major risk group, individuals that currently partake in IDU, are likely to be diagnosed with HCV after the onset of symptoms. By which time, the risk of developing severe liver disease and liver-related causes of death will be increased. It is possible that patients with delayed presentation of symptoms are more likely to be diagnosed in hospitals, rather than in primary healthcare locations, but no research has explored this possibility.

### **9.8.2 What this study has contributed?**

This study has demonstrated that patients diagnosed in hospitals are at significantly greater risk of liver-related causes of mortality within 1 year of detection. This contributes support for the concern that the lack of HCV detection in Scotland and the need to diagnose individuals early. Furthermore, the presence of an HCV specialist centre in a hospital may enhance the chances of survival of patients diagnosed there, rather than in a hospital without immediate access to a specialist.

### **9.8.3 What gaps remain?**

Further studies are needed to follow-up and control for other important factors in delayed healthcare-seeking behaviour, chiefly socioeconomic position. The addition of small-scale residential data would allow further investigations of utilisation and acceptability, relative to geographic access and availability of healthcare.

# 10. Conclusion

## 10.1 Introduction

HCV has been a known global health problem for at least twenty years since its discovery (Choo et al. 1989), though scientists knew of non-A-non-B hepatitis for some years prior (Alter, Hadler, Judson, Mares, Alexander, Hu, Miller, Moyer, Fields, Bradley, and et al. 1990; Kiyosawa et al. 1990; Sampliner, Woronow, Alter, Smallwood, Tabor, Deinhardt, Roggendorf, and Gerety 1984). Now it is well reported in the literature that millions of people are infected, with geographical variation in major risk factors (Alter 2007). At present in the UK, IDU is the dominant risk factor, though historically infection was also possible through blood transfusions prior to the introduction of routine screening of blood donors in the early 1990s (Hutchinson et al. 2006). Targeted screening programmes have resulted in a large proportion of detected infections in persons with a history of IDU and those suffering haemophilia (Dyer 2009; Hutchinson et al. 2004; Scottish Government 2008).

However, vast shortfalls remain in the number of individuals detected compared to the estimated prevalence (The Hepatitis C Trust and The University of Southampton 2005). Many of those undetected individuals are likely to have been part of the 'baby-boomer' generation, some of whom partook in risky behaviour at some point in the 1960-80s during a time of widespread experimentation of substance misuse ((Armstrong, Alter,

McQuillan, and Margolis 2000; Armstrong et al. 2006; Tanaka, Hanada, Mizokami, Yeo, Shih, Gojobori, and Alter 2002). Many will have experimented transiently in adolescence and early adulthood, now living with undiagnosed HCV infection for several decades, but not recognised as a major risk group for targeted screening (Dienstag 2006).

With ageing, the risk of developing complications of cirrhosis 20-25 years (Figure 15.1) after infection and HCC a decade or so later increases markedly (Alberti, Chemello, and Benvegna 1999; Davila, Morgan, Shaib, McGlynn, and El-Serag 2004; El-Serag, Davila, Petersen, and McGlynn 2003; El-Serag, Marrero, Rudolph, and Reddy 2008; Hassan, Frome, Patt, and El-Serag 2002; Massard et al. 2006; Poynard, Bedossa, and Opolon 1997). The chances of successful combination therapy decreases as individuals enter the late stages of HCV infection, by which time their limited options include palliative care or a liver transplant (Perz and Alter 2006). HCV is now a leading cause of cirrhosis and HCC and indicator of the need for liver transplantation (Bosetti et al. 2007; Gerner et al. 2006; Golden, O'Dwyer, and Conroy 2005; Perz and Alter 2006; Perz et al. 2006)).

Therefore, a major task that lies ahead is for the many unrecognised HCV infections to be diagnosed and for people to be referred for specialist treatment that could cure them as early as possible. However, much of the literature on HCV infection charts national prevalence rates, projections of disease burden and medical treatments (Alter 2007; Armstrong, Alter, McQuillan, and Margolis 2000; Armstrong et al. 2006; Deuffic,

Buffat, Poynard, and Valleron 1999; Deuffic, Poynard, Buffat, and Valleron 1998; Dore, Law, MacDonald, and Kaldor 2003; Hutchinson, Bird, and Goldberg 2005; Law et al. 2003; Shepard, Finelli, and Alter 2005).

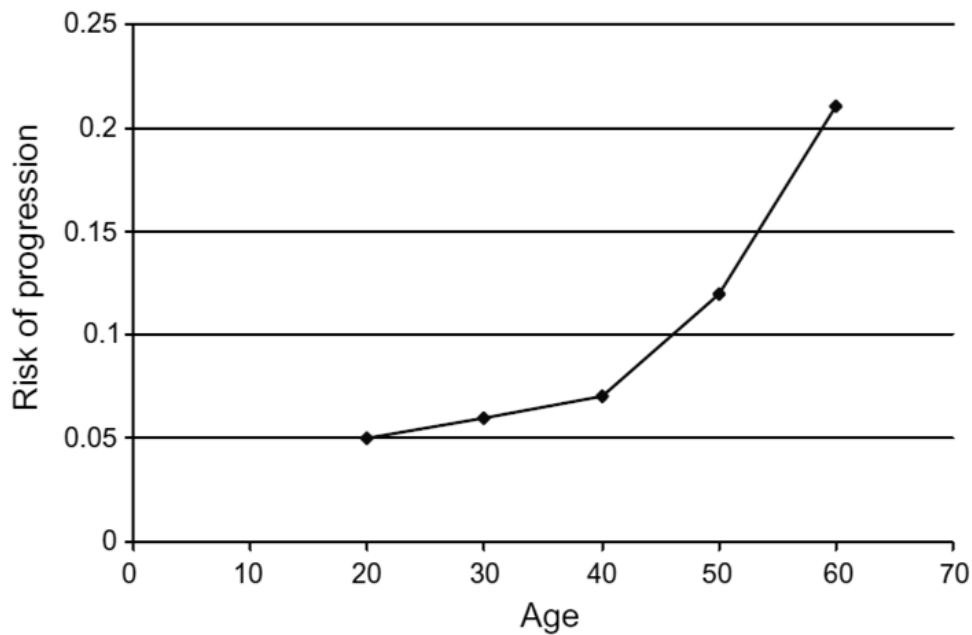


Figure 15.1: 'Effect of age on the risk of progression of hepatic fibrosis in the 4 years subsequent to initial liver biopsy' (Source: (Ryder 2007))

In comparison, the sociological literature on living with HCV and various outcomes along the patient pathway remains scant (Hopwood and Southgate 2003), limited mainly to work in the last five years on some risks of transmission (IDU, occupational, vertical), and more recent emerging literature on HCV awareness and discrimination (Davis, Rhodes, and Martin 2004; Davis and Rhodes 2004; Day, Ross, and Dolan 2003; Golden, O'Dwyer, and Conroy 2005; Hopwood, Treloar, and Bryant 2006; Paterson, Backmund, Hirsch, and Yim 2007; Temple-Smith, Gifford, and Stoov 2004; Temple-Smith et al. 2007).

However, a lack of awareness and discrimination may only be partial explanations for the shortfall in HCV detection relative to the estimated prevalence in the UK. Figure 15.2 illustrates an amended version of the 'HCV iceberg' from an earlier chapter. Most persons infected with HCV are unaware of their condition, therefore unable to proactively seek counselling and treatment, and may be unconsciously putting others at risk of infection. Of those individuals that are diagnosed, they need to be referred to an HCV specialist centre where this counselling and treatment can be obtained. Yet only a proportion of diagnosed individuals are referred. Furthermore, referral is no guarantee of utilisation, with some patients attending but not keeping up with appointments, whereas others do not attend at all. Shortfalls at almost every point on the patient pathway may increase the risk of a lot of people developing advanced liver-related morbidity and mortality.

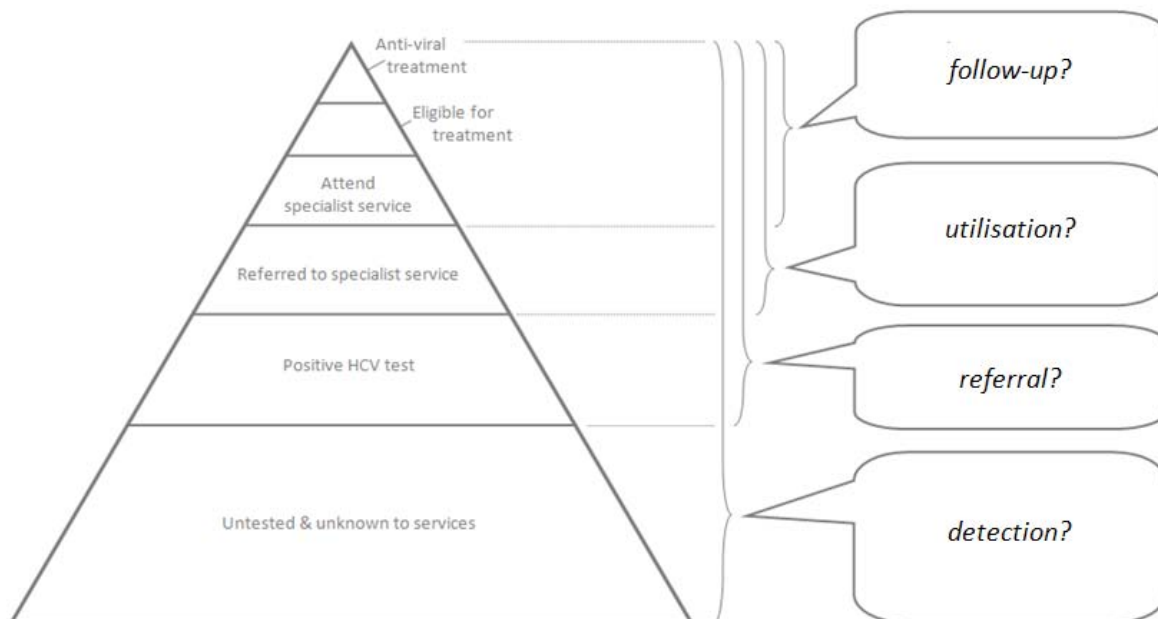


Figure 15.2: Thesis questions 1-3: detection; referral; utilisation



A lack of geographic access to healthcare may be a factor in each of these shortfalls, but in comparison with other public health issues such as cancer and heart disease, this aspect has received little attention so far in the HCV-related literature. The aim of this study was to explore these possibilities in a geographically-delineated region of Scotland, NHS Tayside, which contained marked socioeconomic variation between the densely crowded city of Dundee and the sparsely populated settlements in the rural, remote north and west. To accomplish this aim, chapters 1-3 brought together literature from medicine, epidemiology, sociology and geography in order to tease out several main research questions for further study:

- 1. Does geographic access to healthcare influence the detection of HCV?*
- 2. Are the chances of referral poorer for individuals lacking geographic access to an HCV specialist centre?*
- 3. Are patients with further to travel less likely to utilise HCV specialist centres?*
- 4. Are individuals with poorer geographic access to healthcare more likely to suffer liver-related mortality outcomes?*
- 5. Are chances of survival from HCV infection associated with the type of diagnosing location?*

These questions were addressed in the preceding 5 chapters. In this last chapter, I draw these results together, first by means of summary, followed by reflection upon data and measurement. Some potential implications for policy are suggested, possible opportunities for extending this study are outlined, and rounding off the chapter with some final general remarks on the study as a whole.

## **10.2 Summary of the results**

In this study, measures of travel-time were estimated from secondary data in a GIS to explore the extent that geographic access to healthcare, primary and specialist, has influenced outcomes for individuals infected with HCV in Scotland. Individual-level data was primarily available for NHS Tayside to investigate patterns of detection, referral, specialist healthcare utilisation and cause-specific mortality. A national dataset was also subsequently used to extend the mortality analyses with large samples and details of location at which diagnosis was made. Answering a range of questions and utilising a variety of statistical techniques, this is the first *explicitly* small-scale geographical study of HCV worldwide.

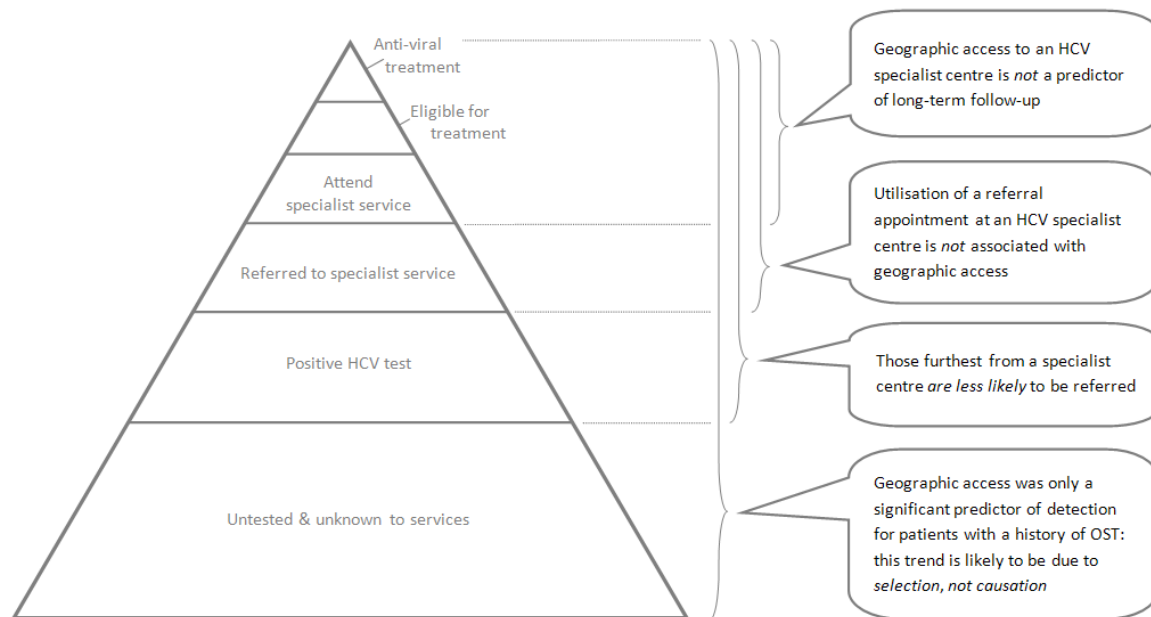
Chapter 4 explored the first research question: ‘does geographic access to healthcare influence the detection of HCV?’ There were two motivating issues for this particular

research question: a) that previous studies had shown that a lack of geographic access to healthcare may result in delayed healthcare-seeking behaviour, thus applicable to the shortfall in HCV detection; b) two recent studies in France (Monnet et al. 2006; Monnet et al. 2008) have asked similar questions of HCV detection, but were limited in their ability to control for IDU risk factors and individual (or small-scale ecological) measures of socioeconomic position.

Using an ecological-study design and Poisson modelling, initial calculations showed HCV detection rates among patients with the furthest to travel to consult their nearest GP were significantly lower in comparison with those with shorter travel-times. This result held even after controlling for sex (men more likely to be detected than women), age group (persons between 25-29 more likely to be detected compared to those aged 15-24 (persons over 40 less likely)), and the Carstairs index, a measure of socioeconomic deprivation (strong positive association with detection).

However, augmenting the models with a measure of OST history produced interesting results, chief of which was to raise attention towards the validity of the previous travel-time association with detection. A lack of geographic access appeared only to be a significant predictor of lower detection amongst individuals with a history of OST, not for those without. The significance of this result was in that it pointed towards the possibility of confounding due to a lack of control for IDU risk factors, which were expected to be most prevalent in more urban areas where travel-times to primary

healthcare are short. The absence of a significant effect for the non-OST sample suggests that this trend, and quite possibly those published by Monnet and colleagues, are an artefact of selection bias. This result is positioned onto the ‘HCV iceberg’ in Figure 15.3, which also illustrates the other results from the first three research questions.



**Figure 15.3: Thesis results 1-3: detection; referral; utilisation**

It is important to note that these results do not mean that geographic access to healthcare is not an issue of significance when discussing the low rates of HCV detection. But in this particular case study, these findings seemed to underline the prior uncertainty over the validity of previous claims (by Monnet and colleagues), rather than substantiate them or their obverse. Were only the detected sample analysed (sensu, the France-based studies), the finding would have been that lower rates of detection were found amongst individuals with the furthest to travel even after going one step further and adjusting the model with a very small-scale measure of socioeconomic

deprivation. That this association varied significantly between individuals with and without a history of OST in a second stage of analyses marked the use of this variable out as an innovative and potentially important extension to previous work.

The history of OST variable was also used in chapter 5, in which the emphasis was on whether a lack of geographic access to an HCV specialist centre was associated with lower chances of referral (question 2). Several hypotheses for why GP referrals could be lower in more rural, remote areas were discussed, including a geographical variation of HCV awareness, potentially more prevalent stigmatising behaviour and attitudes towards IDU, or maybe even a reluctance to refer on medical grounds and/or a knowledge of patient circumstances. In this case, geographic access was calculated as an estimate of the travel-time between patient residence and the HCV specialist centre in NHS Tayside, located at Ninewells Hospital in Dundee.

As expected, logistic regression models showed that those patients with further to travel were less likely to be referred. With this data, it was impossible to attribute support for any of the hypotheses with certainty, though the persistence of the statistically significant travel-time parameters even after augmentation with the history of OST variable suggested that IDU-related discrimination is perhaps less likely. Recent evidence showing the widespread lack of HCV awareness amongst GPs in the UK probably marks this explanation out as the most likely so far.

In chapter 6, the utilisation of HCV specialist healthcare was the main outcome of interest (question 3). Non-attendance has been identified as an important factor for the lack of treatment of persons diagnosed with HCV so far. However, despite poor utilisation rates of numerous other health issues shown to be associated with a lack of geographic accessibility (e.g. (Jones et al. 2008a; Nattinger et al. 1992; Nattinger, Kneusel, Hoffmann, and Gilligan 2001; Nemet and Bailey 2000)); no similar research has yet been conducted for persons infected with HCV.

Non-attendance was measured in two stages: i) patients that failed to attend their first referral appointment with the specialist; but if they made it, ii) the chances of dropping out of follow-up at some point before being formally discharged. Contrary to the hypotheses, logistic regression models showed that the chances of utilisation did not appear to be diminished amongst those with further to travel. Neither were those patients lacking geographic access more likely to be lost to follow-up. In fact, an interaction for the latter trend with age suggested that older patients with further to travel were more likely to stick with the programme, which runs counterintuitive to suggestions in the literature that longer travel-times are likely to exacerbate mobility issues and lower the rates of utilisation (Arcury et al. 2005; Arcury, Preisser, Gesler, and Powers 2005; Nemet and Bailey 2000). As seen in previous studies, a history of IDU was a significant predictor of non-attendance (Bini et al. 2005; Butt, Wagener, Shakil, and Ahmad 2005) and deprivation and IDU history were both positively associated with being lost to follow-up (also seen in (Seal et al. 2007).

In reflection, it is reassuring that long travel-times did not seem to adversely influence the utilisation of the HCV specialist centre in NHS Tayside. There were various explanations for these results. Reliance upon an [widely-utilised] ecological measure of socioeconomic deprivation may have underestimated the extent of difficulties for those in more rural, remote areas where geographic units are larger by necessity and may mask 'pockets' of deprivation as a result (Haynes and Gale 2000). Individual-level measures of socioeconomic position (such as occupationally-derived measures of social class and education), had they been available, might have been able to identify such confounding.

On the other hand, those individuals that were referred regardless of a lack of geographic access may indeed have been relatively more able and/or determined to access treatment for their infection, as has been previously found amongst persons occupying more favourable socioeconomic positions (Armstrong, Fry, and Armstrong 1991; Evans 1993). This suggests the likely presence of selection within the study sample, in which maybe those individuals least likely to attend or lacking the propensity for lots of visits over a sustained period of time and maybe decreased chances of treatment success (and overall benefit) were not referred. Had they been referred, as the recommended guidelines state they should have, rates of utilisation could have been much poorer than observed amongst those with the furthest to travel in this study.

Of course, if the travel-time-detection hypothesis also turns out to be true and a relatively large number of people lacking geographic access to healthcare remain undiagnosed till later, when liver-complications are more severe and may significantly influence physical and mental health, long travel-times and distances may become highly significant in the delivery of HCV specialist healthcare. First, the risk of death from liver-related causes may be elevated for those living further from healthcare as a result of late detection. Second, the severity of the liver-related complications may lead some of these persons into bypassing their local GP, going direct to their nearest hospital instead. In which case, liver-related mortality within a short time-frame following diagnosis might be disproportionately amongst those patients diagnosed in hospitals, not in by GPs.

The last two preceding chapters dealt with each of these hypotheses. Chapter 8 used Cox regression models to model the risk of liver-related death in the NHS Tayside data from Chapter 4. All-cause mortality and drugs-related mortality were also explored for indirect contrasts, the latter of which has previously been shown to be common amongst younger persons infected with HCV (Amin et al. 2006; Mohsen and Group 2001). Analyses showed that older age was a significant predictor of liver-related and all-cause mortality, but not of drugs-related that was more strongly associated with a history of OST. The risk of death from all-causes, liver-related and drugs-related causes was high for patients that were not referred to the HCV specialist centre in NHS Tayside. Importantly, diagnosed individuals with further to travel were not at greater risk of a



liver-related death. All-cause and drugs-related mortality tended to be higher amongst patients living closer to Ninewells Hospital, but the most likely explanation for this observation is that the Carstairs index was an insufficient adjustment for risk in the models.

A further issue with the first set of 'survival' analyses was that the small sample size, which effectively removed the possibility of exploring the risk of death in the short- and long-term following an HCV diagnosis. Additionally, the type of healthcare location in which a diagnosis was made was also of interest. The analyses in Chapter 9 addressed some of these issues. Using Cox regression models to measure association with liver-related and drugs-related mortality, differentiating between deaths within 1 year and between 1 to 10 years following diagnosis, the results showed that the risk of death from liver-related causes within one year of diagnosis was highest amongst those in hospitals compared to primary healthcare (GP practices and GUM clinics). Furthermore, there appeared to be variation between hospitals with and without an HCV specialist centre onsite, with those in the latter faring worse outcomes. For liver-related deaths between 1 and 10 years, the primary/secondary differential persisted but there was no statistical difference between hospitals with or without an HCV specialist centre. This might indicate some sort of 'protective' effect of being diagnosed in a hospital with specialist expertise on HCV on individuals detected at a late stage of infection.

### **10.3 Conclusion and policy implications**

In collation of the literature reviewed, the hypotheses developed and the empirical findings, it can be concluded that this study has made significant inroads into understanding the extent to which geographic accessibility to healthcare has influenced outcomes amongst individuals infected with HCV in NHS Tayside, Scotland. Long travel-times were a significant predictor of low detection rates, but only amongst a risk group that are expected to be most concentrated into urban areas where travel-times are short. Crucially, this suggests that a) previous findings in France were probably confounded by selection bias; b) improving geographic access to primary healthcare is probably not going to improve rates of HCV detection in the UK. These conclusions are supported by later findings showing that the risk of liver-related mortality (a proxy indicator for the presentation of severe liver-complications at diagnosis) was not higher amongst those patients with the least geographic access to primary or specialist healthcare.

Patients living further from a specialist centre had lower chances of being referred, which was likely to be due to a poorer level of HCV awareness amongst GPs in rural, remote areas. A lack of geographic access was not detrimental to any of the other outcomes, including the utilisation of HCV specialist centres.

Significantly, this study also showed in no uncertain terms that the detection of HCV infections is much higher in more deprived areas, which builds towards answering a call by Hutchinson et al (2004) for more research in this regard. Deprivation was also a significant predictor of long-term loss of follow-up in HCV specialist centres, but not for referral, initial attendance or mortality outcomes.

For policymakers, these results may read as reassuring, with broad endorsement of the most evident policy implication raised elsewhere in academic journal articles (e.g. (d'Souza et al. 2004), by activists (The Hepatitis C Trust and The University of Southampton 2005; The Hepatitis C Trust and The University of Southampton 2006), and by action plans (Scottish Government 2005; Scottish Government 2008): the need to raise awareness of HCV and referral protocol amongst the public, GPs and medical staff more widely.

The action already taken in this regard, the "Face-It" awareness campaign was discussed in chapter 2. It is unfortunately regarded as 'very little, very late' by Professor Foster, of the Royal London Hospital. Foster continues:

*"What we have is a rather belated publicity campaign which is not associated with increased funding or improvements in liver services. There is a real danger that this will identify patients for whom there are no resources to treat them."*

(BBC News Online 2004)

Raising awareness will increase not only rates of detection, but rates of referral to HCV specialist centres. As the results of this study showed, those with furthest to travel were less likely to be referred. One partial reason why this might be is that those individuals were not referred because of the potential difficulties in utilising the healthcare available in only specific locations, often centralised into large hospitals in cities. Therefore, raising awareness and increasing referral rates amongst people diagnosed in more rural, remote locations may mean that geographic accessibility will become a key issue in the effective delivery of HCV specialist healthcare.

Hence, a second worthy indication for policy might be to set up a monitoring system for trends in detection, referral and the utilisation of HCV specialist centres at small geographical scales (e.g. Output Areas). Through such monitoring, the NHS will be able to identify communities that are relatively underserved and a re-allocation or redistribution of resources; or individuals to which assistance with transportation or another intervention aimed at improving geographic accessibility to healthcare might be offered if mobility is a difficulty.

On the other hand, these results may be disconcerting for policymakers. A genuine attempt at examining a fairly intuitive hypothesis has reaffirmed that explanations for the shortfall in HCV detection are likely to be complex and multifaceted. The search for policy levers of change must continue if the NHS is to avoid the predicted wave of liver-related morbidity and mortality, coming at huge financial costs and demand for liver

transplants (The Hepatitis C Trust and The University of Southampton 2005). Those undetected individuals with HCV infection need to be diagnosed as soon as possible and given every opportunity to clear this virus quickly, efficiently, and with a minimum of influence upon their social and working lives.

## **10.4 Reflections and further opportunities**

In order to conduct this study, several different types of data were required. ELDIT and the Tayside HCV Clinical Database provided individual-level data on HCV anti-body positive diagnoses and follow-up through referral, utilisation of an HCV specialist centre and cause of death (each where appropriate), which formed the mainstay of each set of analyses bar the last chapter. This data also included information on sex, age at diagnosis, an indication of OST history, date of death and the 2001 Output Area of residence. Each of these variables was important in their own right, allowing more in-depth analyses and some whole research questions to be explored.

This data was essential for all analyses, but was not perfect by any stretch. In the absence of similar data-linkage resources in other NHS healthboards, the geographical extent of the database was NHS Tayside only. This limited the study to small sample sizes and the power of analyses to generalise more widely. There were further issues,

such as the use of OST history as a proxy for identifying patients known to have a history of IDU to the medical profession. Whilst innovative, this also created a second, rather more heterogeneous group that would have comprised several risk groups comprising persons infected through blood transfusions to those who experimented with injecting drugs in early adulthood to others with current IDU behaviour without a history of OST. Self-reported IDU risk used in the utilisation analyses from the Clinical Database may not be significant improvement upon the history of OST, potentially confounded by recall-bias. Larger sample sizes and disaggregated risk group data (e.g. current IDU / past IDU) would represent an interesting further opportunity for research, were data to become available.

Perhaps even more important was the geographical information that was available at the smallest areal unit at which the UK Census is disseminated. Crucially, the Output Area identifier allowed linkage to the Census denominators to enable the first question, and the linkage of the Carstairs index of socioeconomic deprivation and the measures of geographic access to healthcare that were used extensively.

Without this small-scale geographic identifier, this study as it is would not have been possible. The HCV diagnoses data did not contain individual measures of socioeconomic position, such as income, employment, social class, or education, so the data-linkage of an ecological measure of socioeconomic deprivation proved an invaluable asset. One possible critique of this approach would point to the ecological fallacy, in that an

individual-level socioeconomic position is being inferred by a group-level variable (Pearce 2000; Piantadosi, Byar, and Green 1988; Schwartz 1994). The advantage of using Output Areas over alternative boundary-sets is that they are the smallest areal unit available for which the Carstairs index could be calculated, thus marking an attempt to maximise socioeconomic homogeneity (with greater variation probable for larger scales such as postcode sectors).

Similarly, the estimates of geographic access to healthcare were informed by the Output Area identifier. Geometric centroids were used, as is common in research of this genre, to simulate residence on the road network. This is an approximation and arguments could be made that the unit postcode coordinates would have been better. However, access to such a small-scale of geographical information linked with individual data pertaining to such a sensitive health issue would have compromised anonymity. As such, Output Areas were also the smallest geographical scale acceptable for ethical approval. Should strategies around this limitation become available, a refined set of travel-time estimates, potentially including public transport data if it were to become electronically available, would provide further insights into geographic accessibility modelling and outcomes related to HCV infection.

## 10.5 Key findings in summary

- HCV detection was lower amongst those lacking geographic access to primary healthcare, but further analyses suggest this trend is due to selection, not causation
- Individuals with the furthest to travel were less likely to be referred to an HCV specialist centre, compared to those with better access
- Travel-time was not a significant predictor of utilisation of HCV specialist centres, but the samples were likely to suffer selection bias
- Patients lacking geographic access to healthcare were not at greater risk of liver-related mortality, indicating no significant delay
- Patients at greater risk of liver-related mortality were more likely to be diagnosed in hospitals, indicating delays in healthcare-seeking behaviour for reasons maybe unrelated to geographic access to healthcare



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