Non-adherence to medication in schizophrenia: The impact on service use and costs

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Declaration of Authorship

I certify that the thesis I have presented for examination for the PhD degree of the London School of Economics and Political Science is solely my own work other than where I have clearly indicated that it is the work of others (in which case the extent of any work carried out jointly by me and any other person is clearly identified in it).

I warrant that this authorisation does not, to the best of my belief, infringe the rights of any third party.

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Abstract

Schizophrenia is a chronic illness which has severe consequences for the lives of patients and their families. The costs associated with treating individuals with schizophrenia are considerable. This thesis examined the relationship between non-adherence to medication, patient-, environmental- and medication-related factors and the costs associated with health and social care services used and the wider societal costs in treating individuals with schizophrenia. Analysis was undertaken of data from the 1993-4 and 2000 Psychiatric Morbidity Surveys and the Quality of Life following Adherence Therapy for People Disabled by Schizophrenia and their Carers study.

An individual's level of education, having had a recent inpatient stay and alcohol abuse were found to be associated with a greater likelihood of non-adherence in individuals taking antipsychotics. These results were not observed in analyses of individuals taking antidepressants. Common factors associated with non-adherence across individuals taking antipsychotics and antidepressants included experiencing side-effects and severity of illness.

Community-based services were found to be used more by individuals with interruptions in their antipsychotic medication. In this group there may also be additional costs in hospitalisations and overall health and social care services attributable to non-adherence. Benefits to patients may be accrued by enabling health and social care professionals, particularly those working in the community, to encourage medication adherence in individuals with schizophrenia and to provide information on new interventions that are cost-effective in improving adherence.

National Institute of Clinical Excellence (NICE) guidelines for treating individuals with schizophrenia, revised in 2009, address some key findings in my analyses, such as emphasising the role of carers and family members in successful management of the illness, the potentially adverse impact that illicit drug use can have on therapeutic effects and issues around service provision to individuals from ethnic minorities.

Further analysis of data from long-term studies is required to determine the clinical, economic and personal consequences of non-adherence.

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Chapter 1

Introduction

OK. All right. Listen.
Let me join up some of the dots for you.
Let me do some of the maths for you:
Schizophrenia is the worst pariah.
One of the last great taboos...

It is not treatable with glamorous and intriguing
wonderdrugs like Prozac or Viagra.
It isn't newsworthy.
It isn't curable.
It isn't heroin or ecstasy.

It is not the preserve of rock stars and supermodels and hip young authors...
They make movies about junkies and alcoholics and
gangsters and men who drink too much, fall over
and beat their woman until bubbles come out of her
nose but Schizophrenia my friend is just not in the phone book.

Blue/Orange, Act II
Joe Penhall, 2000

The quote above, from the play 'Blue/Orange', captures many of the difficulties that surround schizophrenia – the lack of a cure, the stigma attached to the illness, the degree of isolation potentially felt by people with the illness and the unparalleled lack of understanding of the illness amongst the general public.

Schizophrenia is a severe mental disorder, characterized by profound disruptions in thinking, affecting language, perception, and the sense of self. It often includes psychotic experiences, such as hearing voices or delusions. A recent study estimated that the number of individuals in England suffering from schizophrenia was over 120,000 (Mangalore and Knapp 2007). The World Health Organisation estimated that globally, in the year 2000, schizophrenia was the seventh leading cause of years-of-life lived in disability (WHO 2001). An idea of the difficult lives led by those with schizophrenia is further illustrated by a recent sample of individuals suffering from the illness in Britain. Bebbington et al (2005) found that nearly one-half had

attempted suicide or self-harm, a third had at some point been homeless and one in seven had been in prison.

1.1 Overview

It is evident from research in the UK and elsewhere that the majority of people with schizophrenia need and use a range of health and other services, resulting in high costs to the public purse and (often) to others. One area that significantly impacts on costs is the experience of side effects and non-adherence with treatment. Antipsychotic medications have a high incidence of unwanted side effects associated with poor quality of life, high rates of non-adherence or discontinuation of therapy, and several important comorbidities. Substantial health care resources are used in both managing side effects and managing the consequences of non-adherence or discontinuation of antipsychotic medications.

Weiden and Olfsen (1995) estimated that non-adherence accounts for approximately 40% of rehospitalisation costs for patients with schizophrenia in the two years after discharge from in-patient treatment. Meta-analyses of data from a number of countries concluded that a 50% improvement in adherence would decrease one-year rehospitalisation rates by 12% (Weiden and Olfson 1995). Also, given that anywhere from 25% to 80% of patients at some point in their treatment do not adhere to their medications (Battaglia 2001; Conley and Kelly 2001), the system-wide costs of non-adherence could be substantial.

Schizophrenia patients often require support in daily activities due to the poor personal and social functioning associated with the illness. Patients are likely to have difficulty in finding and holding onto jobs. This also has implications for their families and society at large, as they will be called upon to support patients. Other societal costs accrue from the lost productivity of schizophrenia patients and criminal justice costs associated with violent behaviours that may result from the condition.

So in addition to the clinical and quality of life effects attributable to non-adherence, there are substantial resource implications in the form of higher service use levels and costs that result

from non-adherence. Interventions that are successful in reducing non-adherence rates, including new medications, will have considerable benefit for patients, their families, and the health and social care systems. To date, the majority of pharmaceutical, psychological therapy and psychosocial interventions have been judged based on the degree to which they improve adherence without consideration of their cost-effectiveness (Zygmunt, Olfson et al. 2002). Healey et al (1998) conducted a cost-effectiveness evaluation of adherence therapy and included health, social care and criminal justice costs in their analyses, but this study was limited by a small sample size at the end-point of the study as a result of sample attrition. Hughes et al (2001) highlight the need for more information on the cost consequences of non-adherence to allow economic evaluations to reflect its potential impact. Additionally, evaluations of interventions that may have an impact on non-adherence require a period of observation long enough to allow for adequate assessments of their influence on adherence rates.

This thesis aims to establish factors that contribute to non-adherence in schizophrenia, examine the pattern of health care service use associated with non-adherence and estimate the costs associated with non-adherence. Patterns of service use will be established to determine the impact of non-adherence on resource use and costs. Factors that may impact on the patient's experience include the type of medication prescribed, the type of residential accommodation, general health status, type of family unit, or demographic factors such as age, sex and ethnicity.

1.2 Schizophrenia – prevalence and quality of life

In 1896, Emil Kraepelin established a classification of mental disorders, one of which was dementia praecox (Pull 2002). This illness was given the name schizophrenia by Eugen Bleuler who emphasized the presence of a dissociation of mental functions as the essential characteristic of the illness. The aetiology of schizophrenia is complex with biological, psychological and social factors all thought to play a role in the onset of illness. Genetics are thought to be the most significant factor in the development of the illness, accounting for approximately 80% of risk of onset (Gelder, Harrison et al. 2006). Environmental factors, some of which are experienced prenatally and interact with genetic factors, are also important. Examples of social and

psychosocial factors that may contribute to the onset of schizophrenia are migration, social isolation and stressful life events (Gelder, Harrison et al. 2006).

The relationship between the genes present in people diagnosed with schizophrenia and their development of the illness is not fully understood. It is understood that the illness cannot be attributed to a single gene, although it is not clear if schizophrenia arises from the cumulative effect of several genes or if there are a range of disorders of different genetic makeup that fit within the diagnostic category of schizophrenia (Gelder, Harrison et al. 2006).

Schizophrenia is a severe disorder. Behaviour may be seriously disturbed during some phases of the disorder, leading to adverse social consequences. In the acute phase of the illness, characteristic symptoms include delusions (strong belief in ideas that are false and without any basis in reality), hallucinations, fundamental distortions in thinking and perception, and inappropriate emotions (WHO 2001). These are referred to as positive symptoms. Some patients recover from acute illness, while others will progress to chronic schizophrenia. During the chronic phase of the illness, negative symptoms appear. The most common negative symptoms are social withdrawal, underactivity, lack of conversation, few leisure interests and slowness (Creer and Wing 1975). Once chronic schizophrenia is established, full recovery is extremely unlikely. Other characteristics are disorders of thought and speech, disorders of behaviour, disturbance of emotions and affect, and cognitive deficits (Pull 2002).

In a 14-country study on disability associated with physical and mental conditions, active psychosis was ranked the third most disabling condition, higher than paraplegia and blindness (Üstün and Sartorius 1995). Studies that have followed patients over a long period of time suggest that a minority of patients achieve full recovery, whereas 10-17% required sheltered care and approximately 40% had poor outcome in terms of social adjustment (Gelder, Harrison et al. 2006). Notably, an estimated 30% of patients diagnosed with schizophrenia attempt suicide at least once during their lifetime (Radomsky, Haas et al. 1999).

Because it is a chronic illness, the prevalence of schizophrenia greatly exceeds the incidence. Based on relatively broad diagnostic criterion, the annual incidence of schizophrenia is between 0.16 and 0.54 per 1000 population, while the prevalence is estimated to be between 1.4 and 4.6 per 1,000 population (Jablensky 2003). This prevalence range is observed across countries (Gelder, Harrison et al. 2006). Schizophrenia typically begins in late adolescence or

early adulthood. In a study of the age, beginning and course of the illness, the first psychotic episode began before the age of 30 in 63% of cases (Hafner, Maurer et al. 1993).

There are important gender differences in the incidence, age of onset and severity of schizophrenia as well as differences in the effects of treatment. The incidence of schizophrenia is higher in men than it is in women and women have a later mean age of onset than men (Aleman, Kahn et al. 2003). Fewer women present with the illness between the ages of 15 and 29 as compared to men and a substantial number of women present with schizophrenia in their fifties. There is also evidence to suggest that men experience more severe illness (Aleman, Kahn et al. 2003), and that antipsychotic medications pose more risks for woman than men (Wieck and Haddad 2003).

1.3 The cost of schizophrenia

The total identified cost of schizophrenia in England was estimated at £6.7 billion in 2004/5 (Mangalore and Knapp 2007). This is significantly greater than a 1997 estimate of annual UK costs of £2.6 billion (Knapp 1997). Mangalore and Knapp (2007) estimate that in 2004/5, the cost of schizophrenia in England separated into direct costs of £2 billion and indirect costs of £4.7 billion. The World Health Organisation (2004) estimated that in 2002 the sum of years of life lost due to premature death and the years lost due to disability attributable to schizophrenia in the UK was 85,000 years.

The average annual health and social care (including medications) cost of treating and supporting a schizophrenia patient in the UK has been estimated for 2004/5 at approximately £39,000 and the average annual societal cost at £54,600 (Mangalore and Knapp 2007). A census-based study in four metropolitan areas in Australia, conducted in 1997-1998, estimated the average, per patient, annual societal cost of schizophrenia to be AUS$51,600 (Carr, Neil et al. 2003). The estimated average annual societal cost of schizo-affective disorder was AUS$ 47,900. Based on data collected between 1997 and 2003 in the US, Zhu et al (2008) estimate the average annual medical costs for a patient with schizophrenia to be US$16,100.

Typically, in the UK as elsewhere, in-patient hospital services and community-based (specialist) residential care account for over 70% of direct costs. Curtis (2008) estimated that for a patient with mental illness the UK daily cost of an inpatient stay in an acute NHS psychiatric ward is £219 and in a long-stay NHS hospital ward is £201. The shift towards care in the community has also led to increases in demand for treatment, care and support services that previously would have been provided in long-stay psychiatric hospitals (Pederson and Leese 1997).

The shift towards community-based care has many facets. Crisis Resolution services, for example, provide individuals with serious mental illness who are at risk of requiring psychiatric hospitalisation with flexible, home-based care. Crisis Resolution Teams have been shown to reduce admissions and costs (Johnson, Nolan et al. 2005; Glover, Arts et al. 2006; McCrone, Johnson et al. 2009). Assertive Outreach teams work to keep people in contact with services and support people to continue with their treatment. Early Intervention teams support people intensively in the early phases of their illness. Generic Community Mental Health Teams, another service model providing community mental health care, are composed of professionals from a wide range of disciplines, who provide effective local mental health services primarily for people who use services whose illness is chronic and severe.

Another important cost in treating patients with schizophrenia is the cost of medications. Gilmer et al (2004) estimated the average annual cost of prescribing among 15,962 Medicaid beneficiaries to be US$5,200 in 2004, up 27% from US$ 4,100 in 1999.

Schizophrenia patients often require support in daily activities due to the poor personal and social functioning associated with the illness. Patients are likely to have difficulty in finding and holding onto jobs. Marwaha et al (2007), in a study of people with schizophrenia across the UK, France and Germany, observed unemployment rates of 87%, 89% and 70% respectively. The authors compared these rates to the rates of unemployment in the general population at the same point in time: 29% in the UK, 38% in France and 35% in Germany. Factors contributing to low rates of employment include low educational attainment, employers' negative attitudes about people with mental health problems and self-stigmatising behaviour. The high rate of unemployment among patients with schizophrenia also has implications for their families and society at large, as they will be called upon to provide

informal care to patients. Lost productivity and costs incurred within the criminal justice system are other significant costs associated with the condition.

In relation to their treatment, patients with schizophrenia will experience side effects and are likely at some point to not adhere with their recommended treatment. Antipsychotic medications have a very high incidence of unwanted side effects associated with poor quality of life, high rates of non-adherence or discontinuation of therapy, and several important comorbidities. Additionally, the lack of insight and cognitive impairment that are symptoms of the illness may lead to poor medication adherence by patients. Substantial health care resources are used in both managing side effects and managing the consequences of non-adherence or discontinuation of antipsychotic medications.

1.4 Adherence

1.4.1 Definition and context

The term 'compliance' has been defined as 'the extent to which a person's behaviour coincides with medical or health advice' (Haynes 1979) or 'the degree of conformity between treatment behaviour and treatment standards' (Gaebel 1997). The first of these definitions suggests a degree of paternalism on the part of the clinician, whereas the latter, more recent definition, acknowledges the role of the patient in treatment decisions (Myers and Midence 1998). The greater use of the term 'adherence', instead of 'compliance' also reflects current thinking of less paternalism in treatment decisions. The term adherence is used in this thesis.

Non-adherence can refer to medication, to a therapy or to services (Kuipers 1996). As it relates in medicines, non-adherence covers a range of rates of missing medication across individuals. Some patients may only miss a few dosages while others may consistently not take their medication as prescribed. Non-adherence can also be classified as relating to (a) failure to fill a prescription; (b) filling the prescription but failing to take the medication; (c) taking only a portion of the prescription; and (d) not following the frequency or dose instruction of the prescription (Buckalew and Sallis 1986).

Across illnesses, non-adherence to medication is estimated to account for 135,000 deaths in the US per year (Peterson, Takiya et al. 2003).

Little is known about attitudes of schizophrenia patients towards their medications. The definitions of compliance and adherence given above appear to take a clinical perspective on patient's behaviour towards their treatment. But what are the perceptions of patients? Kuipers (1996) suggests that patients may choose to not adhere to treatment because their perception or experience is that it is inappropriate or inaccessible. It would be desirable to obtain more information from patients as to the reasons why they do or do not adhere to their medications. Some discussion is warranted of how patients' feel about their medications, their understanding of their treatment, and the extent to which they feel committed to their treatment. This perception is particularly important in schizophrenia as, because of the chronic nature of the illness, patients are often on medication on a long-term basis (Fleischhacker 2002). In this thesis, the assumption is made that non-adherence takes place only after patients initially agree to the prescribing of medication to alleviate their symptoms associated with the illness.

1.4.2 Theoretical models

In a chapter of the book 'Patient Treatment Adherence' edited by Bosworth, Oddone and Weinberger, Bowsorth and Voils (2008) present several theoretical models that have been identified to try to understand treatment adherence. These include Locus of Control Theories, Theory of Reasoned Action, Protection Motivation Theory, the Health Belief Model and the Transtheoretical Model. Discussion of these models has sought to describe their application to a variety of health behaviours. These may be relating to preventative behaviours such as breast self-examination, smoking cessation or exercise adherence, to behaviours during treatment, such as medication adherence and behavioural changes sought through interventions to improve adherence. Discussion of theoretical models also covers the various stages of treatment: from seeking and accepting treatment, to starting and maintaining treatment. For the most part, the application of theoretical models in this area has focussed on the understanding of preventive behaviours and the initiation of treatment. There exists less understanding of the maintenance phase of treatment.

Rotter's and Wallston's The Locus of Control Theories

Rotter sets out that there are internal and external dimensions to locus of control. Internal locus of control is the degree to which an individual perceives that reinforcement is contingent on one's behaviour. External locus of control is based on believing that reinforcement is contingent on outside forces such as luck or fate. Wallstron expanded on these concepts by distinguishing external locus of control beliefs which stem from relying on powerful others, such as a physician, as opposed to unknown external forces. Locus of control theories suggest that individuals with good internal locus of control are more likely to adhere to their medical treatment. An individual who believes that by taking their medication as prescribed they will get better is more likely to adhere.

Social Learning Theory and self-efficacy

Bandura's concept of Social Learning Theory is also based around expectations. This theory postulates that human behaviour is determined by expectancies and incentives (Bandura 1977; Bandura 1986). Three main categories of expectancies are described as expectancies about environmental cues, expectancies about the consequences of one's own actions and expectancies about one's ability to achieve a desired outcome. The last of these is termed self-efficacy, and suggests that behaviour is based on both an individual's belief in their ability to perform the behaviour and their opinion of the likely outcomes of the behaviour. The value which the individual places on the desired outcome determines the incentive.

Self-efficacy relates well to medical adherence in that if a patient feels that what is asked of them in managing their health condition is not outside of their ability, they will follow that behaviour as directed. The role of expectation on remaining adherent to medication is, however, less applicable. It is likely that any patient will perceive there to be little difficulty in taking medications. Non-adherence to medication is likely to occur as a result of experiencing side-effects or the patient feeling like they no longer require the medication. In these cases, it is in improving adherence that these concepts can be applied, such as in explaining the consequences of missed dosages.

The Theory of Reasoned Action/Theory of Planned Behaviour

The Theory of Reasoned Action suggests that attitude towards a behaviour and the perception of how others feel about the behaviour will predict whether or not an individual will follow the behaviour. The Theory of Planned Behaviour adds the notion that perception of control over performing a behaviour not only predicts behavioural intention, but will also predict whether or not they actually perform the behaviour. This relates to self-efficacy. The difficulties cited in applying this theory to medical behaviour relate to its inability to explain and account for changes in behaviour over time and the possible divergence between intentions and actual behaviour. It has been found that the type of behaviour and cognitive and personality variables affect the level of consistency between intentions and actual behaviour. By introducing implementation intentions, in effect cues to help determine when, where and how a behaviour is to be performed, can assist in improving adherence. For example, a patient could be told to take their medication each day with their evening meal to help create a pattern for completing the behaviour of medication taking.

Protection Motivation Theory

The Protection Motivation Theory relates to decision making in the face of health threats. The theory suggests that an individual will follow a prescribed behaviour if they are susceptible to a threat, the threat is severe and the individual is fearful of the threat. This theory is particularly relevant in encouraging preventative behaviours, such as condom use, and in medication adherence where physicians can highlight the deleterious consequences of non-adherence.

The Health Belief Model

The Health Belief Model suggests that personal beliefs and perceived susceptibility, severity, benefits and barriers all combine to determine health behaviours (Rosenstock 1966). Susceptibility refers to the subjective perception of personal vulnerability to a particular health problem. Severity is the subjective perception of severity or dangerousness of a health problem and its effects. Benefits are the perceived effectiveness of a range of interventions to

treat the health problem and barriers are the perceived negative aspects of a particular action taken to reduce or eliminate the health problem. These beliefs are thought to be determined by demographic factors and psychological characteristics. The model is most relevant to the context of adopting preventing behaviours and stopping harmful behaviours.

Bosworth and Voil's (2008) review found no evidence that the health belief model has predictive validity in relation to medication adherence. There are studies, however, which do suggest a correlation between dimensions of the health belief model and adherence in schizophrenia. Budd et al (1996) found an association between beliefs around susceptibility and adherence status. That is, those who did adhere to medication perceived themselves to be more susceptible to relapse than non-adherers. Adams and Scott (2000) reported that perceived severity of illness and perceived benefits of treatment explained 43% of the variation in adherence behaviour.

The Self-Regulatory Model of Illness

This model is similar in concepts to those of the self-efficacy model. In a health behaviour context, the model defines there to be three stages of self-regulation: representation of the illness, development and implementation of a plan to cope with the illness and evaluation of the coping mechanism. Individuals are thought to move from one stage to another, in no particular direction. For example, an individual may have a coping mechanism, evaluate it to be ineffective and therefore move back to the stage of development and implementation of a new plan to cope with their illness. This model relates well to acute illnesses, where a cognitive response to a threat to adherence is likely, but does not well explain sustained behaviour in chronic diseases where immediate threats of impact on health are not immediately experienced (for example, hypertension).

The Transtheoretical Model and the Precaution Adoption Model

The Transtheoretical and Precaution Adoption models define stages of behavioural changes. The maintenance stage is only one stage of these. The advantage of these stages is in understanding that the different stages of behavioural change differ significantly. For example

the factors that encourage a patient to begin to follow a prescribed behaviour may be very different from those that encourage maintaining the behaviour in the long term. These models assert that intervention to promote a behaviour should be specific to the stage the individual is in.

The Self-Medication Hypothesis

The Self-Medication Hypothesis states that patients decide to start, adjust or stop prescribed medication according to perceived health needs and that such decisions are conducted intentionally and rationally, given the information available to the patients and their understanding of their condition (Mitchell 2007). Mitchell (2007) asserts that there is evidence that patients with a mental illness do interrupt or stop medication both intentionally and unintentionally, based largely on how they are feeling, which partly supports the self-medication hypothesis.

It is difficult to assess these theories in empirical analysis. One noted deficit of research of adherence in patients with schizophrenia is that the developmental process of decision relating to medication taking is not taken into account (Marland and Cash 2005). Alternative approaches to understating medication taking have been suggested. Demyttenaere (1997) discusses the relevance of considering a medical psychology approach to understand why each individual patient, with his or her specific symptoms, relational context and therapeutic alliance is or is not adherent. Within this approach, the theory of constraints asks the question 'what constrains this patient from more effectively managing his or her condition?'

Weiden (2007) suggests a similar approach in defining a more flexible approach to adherence theory that is more applicable to clinical practice. He suggests five theories regarding medication adherence in patients with schizophrenia. These are:

(1) Adherence is not a clinical outcome and only matters as it interferes with outcome
(2) Adherence problems are often entangled with efficacy limitations of antipsychotic medications
(3) Adherence can be viewed as a behaviour (taking/not taking) or as an attitude (prefers taking/prefers stopping medication)
(4) When considering adherence attitudes, patient beliefs are always reality

(5) Adherence behaviour changes and fluctuates over time and should be considered part of the illness.

The ambiguity arising from the application of these theories can be illustrated by considering responses to the third of these theorems. If adherence is viewed as a behaviour, approaches to improve adherence should address whatever logistic problems prevent patients from taking their medications as prescribed. On the other hand, if adherence is viewed as an attitude, their physician must seek ways to educate and convince the patient of the benefits of their medication. As described by Weiden, non-adherence to medication in schizophrenia typically is not both behavioural and attitudinal.

The theoretical models discussed set out to understand the factors that explain adherence-related behaviours. These cover a range of adherent behaviours from preventative behaviours to adherence during the maintenance phase of treatment in chronic illnesses and responses to improve adherence. These models have led to successful strategies, primarily in the area of eliciting healthy behaviours. But these changes in behaviours are often not maintained. Models which further focus on the understanding the behavioural responses to being in the maintenance phase of prescribed medications in chronic diseases are needed. Such models will encourage the development of strategies of intervening to prevent maintenance phase non-adherence before it occurs.

1.4.3 Prevalence of non-adherence in schizophrenia

Higher rates of non-adherence are likely in chronic diseases, such as schizophrenia, where medication may be required to be taken indefinitely. Comparing non-adherence rates across studies is difficult due to the range of methods used. For example, Cramer and Rosenheck (1998) reviewed 24 studies in which the methods used to assess non-adherence included patient interview, clinical assessment, urine or blood markers and pill counts, and found non-adherence to range from 10 to 76%. The mean rate of non-adherence across these studies was 42%. Fenton et al (1997) reviewed 15 studies published between 1983 and 1996 which ranged in the period over which they assessed non-adherence from one month to two years. They found non-adherence to range from 24 to 88% with a median of 55%. A review by Lacro

(2002) found rates of non-adherence ranging from 4% to 72% with a mean of 41%. This review is described in greater detail later in this chapter in an overview of factors associated with non-adherence.

The use of depot injections of antipsychotics to reduce rates of non-adherence does not eliminate the problem of non-adherence. A study by Kane (1996) found that one in five patients relapsed when receiving long-acting depot injections. A meta-review of depot antipsychotic drugs, based on studies observing in-patients and patients in the community, found no statistically significant difference in relapse, attrition and adverse effects between depot antipsychotics and oral antipsychotics (Adams, Fenton et al. 2001). This, however, may be due to the fact that those patients participating in trials were required to be reasonably compliant with oral medications, and thus the benefits of depot medications may be underestimated as compared to studies that included patients likely to be non-adherent to oral antipsychotics.

The rates of non-adherence in other chronic diseases are comparable to those observed in schizophrenia. A mid 1990s study found that drugs for hypertension are discontinued within six months by approximately 55% of patients in the UK (Jones, Gorkin et al. 1995). Non-adherence rates for medication for rheumatoid arthritis have been estimated as being 64%, with 24% of these being consistently non-adherent (Viller, Guillemin et al. 1999). Briesacher et al (2008) recently reviewed US health care claims data to compare the rates of adherence across seven conditions. They found that, based on the sum of each day's supply of medications, the rate at which patients missed 20% or more of their medication was 30% for patients with hypertension, 50% for those with osteoporosis and 40% for those with type 2 diabetes. Non-adherence rates of between 0-60% have been found in a review of studies of adherence in patients with rheumatoid arthritis (Harrold and Andrade 2008). For patients taking antibiotics, a 50% non-adherence rate has been reported (Ley and Llewellyn 1994). Rates of non-adherence vary widely in depression, likely in part because the illness can be present over a short or long term. Recent evidence estimates the six month non-adherence rate of patients taking SSRIs to be approximately 40-60% (Nemeroff 2003; Sheehan, Eaddy et al. 2005; Cantrell, Eaddy et al. 2006).

1.5 Factors associated with non-adherence

Several factors are thought to contribute to non-adherence in patients with schizophrenia. For example, the type of medication is thought to be important due to differences in the nature of side effects associated with each. The older generation of antipsychotic medications, the so-called 'typicals', elicit the following side effects: Parkinsonian side effects (including tremor, hypersalivation), akinesia (slowing of movements), acute dystonic reactions (characterised by dramatic muscle spasms), akatgusua (characterised by an inner subjective restlessness), tardive dyskinesia (a movement disorder), anticholinergic side effects (including dry mouth and constipation), diminished sexual function and weight gain (Bentall, Day et al. 1996). The newer antipsychotic medications reduce neurological problems commonly experienced with typicals, but many of the other side effects, such as weight gain and sedation are common to both classes of antipsychotics (Fleischhacker 2002).

Fenton et al (1997) categorise the range of factors affecting adherence into patient-related, medication-related, environmental factors, and psychodynamic considerations. They identify patient-related factors as: demographic characteristics such as gender and ethnicity, illness characteristics such as age at onset and duration of illness, illness severity and subtype (e.g. paranoid schizophrenia), cognition or memory, insight, other health beliefs (i.e. attitudes towards medication), subjective well-being, and alcohol and drug use. The medication-related factors reviewed were side effects, dosage, agent, route, and complexity of regimen. Environment factors considered were: family and social support, practical barriers (e.g. financial burden prevented patient from filling prescription), physician-patient relationship, attitude of staff, interventions, reinforcement, education, and memory enhancement. Psychodynamic considerations include: psychological meaning (e.g. feelings about the role of authority and control in the prescribing of medications), psychological homeostasis (e.g. relationship between delusions and self-image), and transference/countertransference (i.e. attitudes towards the prescriber as an authoritarian figure).

There is uncertainty as to the impact that cognitive impairment, a symptom of psychotic illness, may play in non-adherence in patients with schizophrenia (Buchanan 1996). Pinikahana (2005) points out that non-adherence rates with medicines for general medical conditions such as diabetes and arthritis, and antibiotics, which do not impair cognitive

function, have similar rates of non-adherence as those observed in patients with schizophrenia.

To identify previous empirical studies assessing factors associated with adherence, structured searches in MEDLINE and PsychInfo were run using the search terms '(antipsychotic or psychosis or psychotic) and (adherence or compliance)' to identify relevant empirical studies. The initial search was restricted to studies published in 2000 or later. Other studies were identified by reviewing the references from an initial selection of studies. The literature search identified five reviews. Empirical studies identified by the search and included in one of the reviews were not considered on their own so as to avoid double counting. The search identified 43 empirical studies in addition to the four reviews. From each of the identified studies, information was extracted on the date, location, sample size, sample characteristics (whether patients were inpatients, outpatients or both; and whether they had experienced psychosis or diagnosed as schizophrenic), method of assessing non-adherence, factors found to be significantly associated with non-adherence, and factors found not to be associated with non-adherence. The factors included in the empirical analyses are based on these variables previously considered in this literature. These studies are listed in appendix 1.

1.5.1 Heterogeneity of methods

The samples under observation across the studies differed along several dimensions. In particular, treatment settings, diagnoses, method of non-adherence assessment, and the length of time over which non-adherence was assessed differed across studies. A majority of the studies sampled patients with schizophrenia and schizophrenia-related illnesses. The remainder, along with the reviews, defined their samples more broadly, by looking at patients with psychosis.

The length of time over which adherence status was assessed in the previous studies ranged from one month to five years. Assessment of non-adherence was by a range of methods: self-report, medical records, and clinical assessment. As in the Psychiatric Morbidity Surveys (PMS), which I use later in this thesis to support new empirical analyses, in 11 of the 43 empirical studies, the assessment of adherence relied exclusively on self-reported information. In a further fourteen, self-reported information was combined with the opinions of a family

member, a treating physician or a case-manager. Additional information may be helpful, but may also be problematic. Kampman et al (2001) found only a 0.50 correlation in adherence assessments between patients and doctors. Also, the investment in finding a successful treatment may bias the opinion of physicians (Diaz, Levine et al. 2001).

It would appear that few studies corroborate self-reported adherence with pill counts or physiological data (Zygmunt, Olfson et al. 2002). These methods were used in only five of the 40 empirical studies reviewed. All measures of adherence have their drawbacks (Thompson, Kulkarni et al. 2000; Coldham, Addington et al. 2002; Osterberg and Blaschke 2005), but only self-report will be feasible in a large scale survey. The methods used in empirical analysis of the factors associated with non-adherence in patients taking antipsychotics are discussed in more detail in the following chapter.

The heterogeneity of results from previous studies may also be due to changes in treatment regimes across time and location. The newer atypical antipsychotics have been shown to be associated with different profiles of side-effects (Geddes, Freemantle et al. 2000), and this may influence the association between side effects and non-adherence. A trend towards lower non-adherence in patients receiving atypical medications has been observed elsewhere (Olfson, Mechanic et al. 2000; Sartorius, Fleischhacker et al. 2002). Chapter 3 of this thesis examines trends in prescribing in schizophrenia in greater detail.

1.5.2 Summary of findings

The literature search yielded five reviews of studies empirically assessing factors potentially associated with non-adherence (see Table 1.1; (Fenton, Blyler et al. 1997; Kampman and Lehtinen 1999; Lacro, Dunn et al. 2002; Nose, Barbui C et al. 2003; Voruganti, Baker et al. 2008). The studies were published between 1997 and 2008. The method by which the authors of the reviews attributed significance to factors based on the results across the studies differed markedly. For example, Lacro et al (2002) determined the key factors to be those identified as being statistically significant in 50% or more of the studies included in the review. Voruganti et al (2008) on the other hand, did not explicitly state their criteria for assessing the balance of evidence on the influence of factors on non-adherence but appear to base this on significance observed in the vast majority of the studies included in their review.

Despite the limitations in comparing assessments across the reviews, the findings do reveal some consistencies (Table 1.1). Drug and/or alcohol abuse and lack of insight were identified as key factors in four of the five reviews. In the one review where lack of insight was not mentioned, patient attitudes and beliefs, which may be comparable to lack of insight, was deemed to be significantly associated with non-adherence. In three of the five reviews symptom severity was identified as a key factor in association with non-adherence to medication.

Unlike the evidence reviewed by Voruganti et al (2008) there is some evidence of a greater risk of non-adherence with typicals relative to atypicals. The evidence, however, is not unanimous. This may be due to the fact that the range of experience of side effects within medication type may also differ. Olfson et al (2000) report improved adherence within three months of discharge for those patients prescribed an atypical antipsychotic, though other evidence that looked at adherence over the previous year did not show this relationship. A US study by Dolder et al (2002) compared non-adherence rates in haloperidal and perphenazine (typicals) with risperidone, olanzapine and quetiapine (atypicals) over a 12 month period and found no significant associations between non-adherence and type of antipsychotic or between adherence and age, gender, ethnicity or diagnosis. A study conducted in Spain comparing olanzapine (an atypical) with risperidone (an atypical) and haloperidol (a typical) found that non-adherence, as measured subjectively by the treating psychiatrist, was significantly lower in patients taking olanzapine relative to risperidone and haloperidal (Garcia-Cabeza, Gomez et al. 2001).

A large US study of Medicaid recipients in Florida found that the class of antipsychotic, age, sex, ethnicity and substance misuse were all associated with adherence rates over a 2-year period (Becker, Young et al. 2007). Those prescribed atypical antipsychotics were found to have higher adherence rates as compared to those patients prescribed typical antipsychotics. Higher rates of adherence were observed amongst patients in the higher age groups, and among men, those of White ethnicity and those without co-occurring substance misuse.

Table 1.1: Factors associated with non-adherence – Reviews identified in literature search. '+' denotes positive relationship; '-' denotes negative relationship; and 'ns' denotes not deemed significant as defined by study authors

Factors	Fenton et al., 1997 Not stated	Kampman et al., 1999 15 studies	Lacro et al., 2002 10 studies	Nose et al., 2003 103 studies	Voruganti et al., 2008 7 studies
Age	Ns		ns	-	
Sex: Male	Ns		ns	+	
Drug and/or Alcohol abuse	+	+	+	+	
Unemployed				+	
Income	Ns				
Education	Ns		ns	-	
Ethnicity	Ns		ns		
Lack of insight	+	+	+	+	
Married or family support		+	ns	+	
Side effects	+	+			
Typical vs atypical meds					ns
Low social functioning				+	
Cognitive impairment		ns			
Poor therapeutic alliance			+	+	
Attitudes/beliefs					+
Cost					+
Life events					+
Symptom severity	+	+		+	
Medication dosage	+		+		
Duration of illness			-		
Inadequate discharge planning			+		

A recent study in Brazil, utilising structured and semi-structured survey questions, asked patients to identify the motivations for their medication-taking behaviour (Rosa, Marcolin et al. 2005). The authors used the Rating of Medication Influences scale to assess the backgrounds of patients and their attitudes towards their medications. The main reason for maintaining adherence to medication was 'perceived day-to-day benefit'. This was identified by 88% of patients. Forty percent of patients felt there was no reason for non-adherence, while 'inconvenience of side-effects' was identified by 36% of patients.

A novel study by Marland and Cash (2005) used qualitative methods to get at the reasons why patients with schizophrenia did not adhere to medication. They found that medication taking decision-making in schizophrenia is not unique, though there may be particular difficulties associated with the illness that make it difficult for patients to progress through developmental patterns to a perceived optimum position which balances the benefits and disadvantages of medicine taking. These stages may include the 'experimental-reflective' stage which involves patients experimenting to optimize the balance between quality of life and the consequences of medication taking; and the 'direct-reactive decision making' stage which is reflected by difficulty linking discontinuation of medication with its consequences. Patients may also be 'deferential-compliant decision makers'. These patients defer decisions about medication taking to their physician and will do whatever their physician tells them is best. Results suggest that adherence is more strongly established for those patients who go through the 'experimental-reflective stage' as compared to those whose decision making is 'deferential-compliant'. Further, the authors found that schizophrenia patients who experience a 'direct-reactive' stage will do so for a longer period of time as compared to patients with asthma or epilepsy. This may be due to the delay in the onset of adverse consequences of non-adherence and/or impaired cognitive insight which is characteristic of schizophrenia.

Rummel-Kluge et al (2008), while not conducting empirical analysis considering how factors associated with non-adherence interacted with each other, did conduct a large survey of psychiatrists in Germany to determine the factors they thought most related to non-adherence. A total of 669 psychiatrists participated. Each was asked to evaluate the compliance in ten consecutive patients over a ten day period. Due to some of the psychiatrists not completing the survey for a full ten patients, a total of 5,729 patients were assessed in the survey. The psychiatrists judged a lack of insight into the need for prophylactic medication, a lack of

insight/denial of illness and embarrassment at taking medication every day to be the factors most strongly contributing to non-adherence.

1.6 The economic impact of non-adherence

In addition to the clinical and quality of life effects attributable to non-adherence, there are substantial resource implications in the form of higher service use levels and costs that result from non-adherence. To assess the evidence relating to costs attributable to non-adherence in patients with schizophrenia, a search of PubMed was conducted using the medical subject headings 'patient compliance', 'schizophrenia' and 'cost or cost analysis'. The search identified 26 studies. A search of PsychINFO within the Bath Information and Data Services using the search terms '('cost' OR 'cost analysis') AND ('adherence' OR 'compliance') AND ('schizophrenia' or 'antipsychotic')' identified a further 26 studies. The criteria for inclusion of studies in this review were that a study (i) either attempted to approximate the cost of services or resource use, or reviewed studies that did; and (ii) undertook an evaluation of the impact of non-adherence on the cost of services or use of services. These criteria identified eight relevant studies.

Weiden and Olfsen (1995) estimated that non-adherence accounts for approximately 40% of rehospitalisation costs for patients with schizophrenia in the two years after discharge from in-patient treatment. Meta-analyses of data from a number of countries concluded that a 50% improvement in adherence would decrease one-year rehospitalisation rates by 12%. The authors based their analysis on data from the US National Institute of Mental Health 1986 Client/Patient Sample Survey and published estimates of the rate of non-adherence reported in published prospective studies. Their analysis included an estimate of the hospital cost burden resulting from non-adherence. This cost was estimated at US$705 million in the first two years following discharge from hospital for an acute schizophrenia admission.

Loosbrock et al (2003) used an US employer claims database to compare the costs of patients with continuous antipsychotic treatment to those who had gaps in medication over the course of a year. Patients with gaps in medication of less than two weeks over the course of the year

had significantly lower costs than those with less than 250-days exposure to antipsychotic medication during the year.

A study by Svarstad et al (2001) based non-adherence assessment on whether or not patients picked up their prescribed medication at a pharmacy. They observed that those patients deemed to be have irregular medication use had approximately US$1,700 higher mean annual hospital costs than the regular medication users. This difference was statistically significant.

A significance association between non-adherence and direct medical costs was also observed by Glazer and Ereshefsky (1996). They used published estimates and clinical experiences judgements of non-adherence rates to compare various antipsychotic medications in the outcome of costs associated with relapse.

Theida et al (2003) performed a review that sought to identify studies that looked at compliance, relapse, and economic costs. Their review identified five studies that 'either estimated the direct cost-benefit from improved levels of drug compliance in schizophrenia or attempted to bring explicit measures of compliance levels into an overall economic consideration of antipsychotic drug therapy'. Two of the five studies they identified were not picked up by the search performed for this thesis. However, neither of these studies explicitly considered the effect of non-adherence on costs. A US based study by Palmer et al (1998) considered discontinuation of medicine due to adverse effects or a lack of response, while Davies et al (1998) considered dropout rates as a proxy for non-adherence.

A large US-based study by Weiden et al (2004) observed that measures of partial adherence suggested that there is a direct link between the proportion of medication missed and the probability of rehospitalisation in a sample of patients with schizophrenia. They found that even gaps in medication taking of 1 to 10 days over a one year period were associated with twice the odds of hospitalisation. Their analysis indicated that the greater the level of non-adherence along a continuum, the greater the risk of rehospitalisation. These results were consistent across methods of assessment of partial adherence.

Another large US study of Medicaid recipients that examined the impact of the degree of adherence on health, social care and criminal justice costs through a series of one-way analyses of variance found that, in separate analyses looking at patients prescribed typical or

atypical antipsychotics, higher total costs were significantly associated with lower rates of adherence (Becker, Young et al. 2007).

Eaddy et al (2005) studied the resource use implications of non-adherence for a group of patients with schizophrenia or bipolar disorder. Patients were judged to be partially adherent, where the degree of adherence was estimated as the ratio of the total days for which reimbursement of prescribed therapy was claimed to 365 days (the length of the period under study), if they had claims for less than 80% of days during the year. Partially adherent patients were significantly more likely to have had an inpatient hospitalisation during the study period.

1.7 Policy relevance of the analysis

The results and conclusions drawn from my analyses have potential relevance for a range of policies and so, potential implications for patients, their health professionals and the health care system.

The analysis of factors associated with non-adherence and a discussion of whether or not the results of this analysis are consistent with theoretical models explaining non-adherence will be beneficial to identify those initiatives, be they clinical or behavioural, that are likely to assist patients in being more adherent to their antipsychotic medication. It will also identify those areas for further research which will further illuminate the factors behind non-adherent behaviour.

Current policy responses to non-adherence include patient-centred compliance therapy and behavioural training, family behavioural therapy, and community-based interventions that provide strong and supportive social networks, close monitoring of clinical status and provision of stable housing (Kuipers 1996; Zygmunt, Olfson et al. 2002). Therapies which develop relationships between patients and therapeutic staff are also effective in improving compliance (Kuipers 1996). Interventions that are successful in reducing non-adherence rates, including new medications, will have considerable benefits for patients, their families, and the health and social care systems.

For NICE, the body within the UK health care system entrusted with evaluating the cost-effectiveness of antipsychotic medication and making recommendations about their use, this thesis provides data on another aspect of costs that could potentially be included in evaluations. The thesis estimates the potential savings that may arise from reductions in health and social care service use costs attributable to improvements in adherence. Hughes et al (2001) highlight the need for more information on the consequences of non-adherence to allow economic evaluation to reflect their potential impact and my thesis identifies some of the issues involved in attempting to do this with antipsychotic medication.

These issues will also have relevance for health professionals who treat individuals with schizophrenia in providing them with information that they can use, in addition to clinical information and their clinical judgement, in making prescribing choices.

1.8 Hypotheses and research questions

The theoretical models that have been put forward to describe the process of adhering to recommended health behaviours cover the prevention of illness and initiation of treatment as well as, to a lesser extent, the management of illness. Here my interest in non-adherence to medication is on this latter phase. Based on these theoretical models and the reviewed literature, my research hypotheses are as follows:

1. Where adherence to medication is driven by attitudinal factors, the degree to which an individual feels threatened by the consequences of non-adherence, reflected by the severity of their illness and their level of insight into their illness, is a key factor in encouraging adherence.
2. For some individuals, medication-taking behaviour is primarily the result of external factors that either encourage or discourage adherence. Here I include social support and the support of health care professionals as encouraging factors and the presence of drug or alcohol abuse and the experience of side effects as discouraging factors.
3. In individuals taking antipsychotic medication, non-adherence to medication is likely to be associated with higher health and social care service use costs due to the worsening of symptoms associated with discontinuation of medication.

The thesis aims to test these hypotheses by establishing which factors contribute to non-adherence, examining the pattern of health care service use associated with non-adherence and estimating the costs associated with non-adherence in schizophrenia.

In attempting to explore the relationships between non-adherence, resource use and costs, and other factors, it is likely to be the case that these relationships are specific to the type of medication that has been prescribed. In order to better understand these relationships in individuals taking antipsychotics, it is necessary to determine how these relationships differ in this patient population as compared to non-adherence to other medications. To facilitate this comparison, analyses will be conducted to determine the nature of the relationships between non-adherence to antidepressant medication, resource use and costs, and other factors. The results of these analyses will allow me to draw conclusions as to the impact of non-adherence to medication that is specific to those individuals prescribed antipsychotics.

Questions to be addressed

At what rate is treatment with antipsychotic medications discontinued and how is this linked to the experience of side effects?

Once discontinuation of antipsychotic medication occurs, what are the implications for how health care resources are used and at what cost?

What factors impact on the relationships between non-adherence to antipsychotic medications and resource use and costs and are these factors specific to this patient population?

1.9 Thesis structure

A brief outline of the structure of the remainder of the thesis is as follows:

Chapter 2 will present and justify the methods used in the research. The methodological foci are (i) data sources; (ii) defining patients (iii) measuring non-adherence; (iv) costing methods; and (v) statistical analyses.

Chapters 3 and 4 will address the research question of the nature of the associations between non-adherence, service use, and costs. **Chapter 3** will present results from analysis of the 1993/4 Psychiatric Morbidity Surveys (PMS). **Chapters 4** will build upon the previous findings by assessing the associations over time. This involves analysis of data from the Quality of Life following Adherence Therapy for People Disabled by Schizophrenia and their Carers (QUATRO) study, a multi-national randomised controlled trial which evaluated an adherence therapy intervention for people with schizophrenia.

Chapter 5 will compare the significance of non-adherence in schizophrenia and depression. Analysis of the 2000 PMS analysis will provide the context for assessing the potential for containing costs given the nature of the association between non-adherence and costs. It will determine if the costs attributable to non-adherence, and therefore the potential savings, differ across the two illnesses.

Chapter 6 will summarise the findings and present the policy implications of the findings in the context of current UK mental health policy. Conclusions will also be presented.

Chapter 2
Methods and data

In this chapter I aim to set out the methods used to address the research questions in the empirical analyses contained in this thesis. A range of methodological issues are discussed. These include the method used to define a sample, the potential options for measuring non-adherence and costing methods. I then briefly describe the datasets that were used in the analyses, indicating key features of each. In discussing the methodological issues of the analyses, reference is made to the literature search described in the introductory chapter. The last part of the chapter is a description of common statistical analytical methods that arise in each of the empirical analyses.

In looking at the relationship between non-adherence and service use costs, the aim was to conduct empirical research based on nationally representative UK data which used a fully robust measure of adherence and collected a broad range of data on health and social care service use and other potential costs such as informal care, time off work and criminal justice costs. By using nationally representative data, the results of the analyses would be relevant within a public health context (Boslaugh 2007). To date, much of the research describing the impact of non-adherence in schizophrenia is based on local data (Thieda, Beard et al. 2003). It would also be advantageous to use longitudinal data as these would provide clearer evidence as to the nature of associations between the variables of interest. The resources required to undertake primary data collection in this way would be quite substantial and thus the obvious choice was to use previously collected data that contain as much of the relevant information as possible.

2.1 Defining a sample

This thesis sought to identify samples of patients who were diagnosed as having schizophrenia and were taking antipsychotics. In identifying patients, those with schizoaffective disorder were also included. Henceforth, the single diagnosis label of

schizophrenia will be used to refer to patients with either schizophrenia or schizoaffective disorder.

A majority of the studies identified in the literature review sampled patients with schizophrenia and schizophrenia-related illnesses. The remainder, along with the reviews, defined their samples more broadly, by looking at patients with psychosis. In reviewing data, it is apparent that in some cases diagnostic information is not available, incomplete or identified the primary diagnosis only. It is therefore difficult, in some cases, to confirm what proportion of patients had a diagnosis of schizophrenia. Therefore, identifying and including those patients who were prescribed antipsychotic medication at the time they were recruited into the study seemed to be the most appropriate method for defining a relevant sample in my analysis, rather than relying on diagnostic data. The majority of these patients will have schizophrenia or have experienced a psychotic episode. Others will have a primary diagnosis for another mental illness, such as bipolar disorder, for which antipsychotic medications are now prescribed.

The physician practice of prescribing a drug or medical device for a purpose different from one of the indications for which the product is licensed is referred to as off-label prescribing. Off-label prescribing has taken place with antipsychotics for many years, although it is difficult to determine when it commenced. Antipsychotics are also now licensed for use in treating bipolar disorder (NICE 2006). Using data from 1994 to 2001 from the UK, Hodgon and Belgamar (2006) looked at the rate of off-label prescribing of atypical antipsychotics within patients in secondary care. They found that, averaged over the study period, just under 60% of their sample had a diagnosis of schizophrenia or schizophrenia affective disorder. Based on ICD-10 diagnosis codes, 18.4% of patients prescribed atypical antipsychotics had a diagnosis of a mood disorder (bipolar disorder is one of the mood disorders), 12.4% an organic mental disorder diagnosis and 4.0% were diagnosed as having a personality disorder. Analysis of data from a population-based study in the Canadian province of Manitoba found that the proportion of patients who were prescribed an antipsychotic and had a diagnosis of schizophrenia declined from 65% in 1996 to 42% in 2006 in the 19 to 35 year age group and from 63% to 58% between 1996 and 2006 in the 36 to 65 year age group (Alessi-Severini, Biscontri et al. 2008). Medical and hospitalisation files were used to identify diagnoses in this study. A US study of non-institutionalised antipsychotics users observed that in 1996-1997, 8% reported having a mood disorder without comorbid schizophrenia, and this rate rose to

22% by 2004-2005 (Domino and Swartz 2008). Throughout the study period, approximately 18% of antipsychotic users reported having anxiety spectrum disorders without schizophrenia or mood disorders. Generally, estimates of off-label prescribing are difficult to obtain as it is often not recorded in a patient's notes and is associated with increased liability for physicians (Hodgson and Belgamwar 2006). The dataset used in my analysis - which does not specifically identify individuals based on a diagnosis of schizophrenia - was from interviews that took place in the early 1990s and the data above suggests that at that time the majority of individuals prescribed antipsychotics would have a diagnosis of schizophrenia.

In the UK it is now the case that the majority of patients with schizophrenia receive care in the community (Mangalore and Knapp 2007). Several previous studies which assessed non-adherence to medication in patients with schizophrenia restricted their samples to inpatients only. Of the studies identified in the literature review reported on in chapter one, eight of 48, or 17% of studies, included inpatients only. The datasets analysed in this thesis either included both inpatients and outpatients or focused on outpatients only. Secondary analyses included homeless individuals.

2.2 Measuring non-adherence

Different options exist for assessing adherence. These include objective measures such as pill counts, prescription renewals, blood tests, or medication markers. Alternatively, assessments of adherence may be asked of patient or their clinicians. No method is without its limitations, however (Cramer and Rosenheck 1998; Thompson, Kulkarni et al. 2000; Diaz, Levine et al. 2001; Kampman, Lehtinen et al. 2001; Coldham, Addington et al. 2002). Pill counts may not detect alternating under- and over-use of medication or discarding of pills and will not capture variations in the timing and duration of missed dosages (Hughes, Bagust et al. 2001).

Relying on prescription renewal information will be effective only if patients use a single source for filling their prescriptions, and if there is a system in place to record all changes in medication and dosage. Blood tests may be misleading as plasma levels can vary widely among patients taking the same dose, and taking doses a few days before a test raises drug levels reasonably close to target. Medical markers, such as riboflavin, are not quantitative.

Assessments by patients may be subject to memory deficits, or distorted due to the level of psychosis, use of illegal substances or denial of illness. Because some patients are unaware of mistakes they are making in their medication regime the prevalence of non-adherence in studies where self-reporting is used will tend to be underestimated (Byerly, Thompson et al. 2007; Velligan, Wang et al. 2007).

Clinical assessments of adherence may be subject to potential bias caused by the clinician's investment in finding a successful treatment (Diaz, Levine et al. 2001). The literature is conflicting with regards to the consistency between patient self-assessment of adherence and adherence as estimated by their physicians. Such an approach is supported in some studies (Kampman, Lehtinen et al. 2001; O'Donnell, Donohue et al. 2003), although a study by Kampman et al (2001) found only a 0.50 correlation in adherence assessments between patients and doctors. Another difficulty observed in the literature is in judging adherence in a clinical trial setting. It has been observed that patients who agree to participate in a clinical study of antipsychotic medications are more likely to adhere to medication and general treatment plans, suggesting a link between consent to research and compliance with treatment (Barnes 2002).

Of interest is how non-adherence has been assessed in previous studies in this area. A structured literature search was described in the previous chapter identifying 43 empirical studies and five reviews. The samples under observation in the previous literature differed along several dimensions. With respect to non-adherence, assessment was by a range of methods: self-report, medical records, and clinical assessment. In ten of the 43 empirical studies (23%), the assessment of adherence relied exclusively on self-reported information. In a further 18 (42%), self-reported information was combined with the opinions of a family member, a physician or a case-manager to arrive at an assessment of adherence. Additional information of this kind may be helpful, but may also be problematic because of the inconsistencies described above. A study of primary care patients prescribed antidepressant medications for 12 weeks or more (defined as maintenance phase) found a 72% agreement between dichotomous classification based on self-reported adherence and adherence assessed from pharmacy refill data (Aikens, Nease et al. 2005). It would appear that few studies corroborate self-reported adherence with pill counts or physiological data (Zygmunt, Olfson et al. 2002). This method was used in only three of the 43, or 7%, of empirical studies reviewed.

It has been pointed out that self-report methods are generally the most cost-effective and time-efficient (Thompson, Kulkarni et al. 2000). Also this may be the only feasible method for collecting adherence information in a large scale or population-based survey. Lecomte et al (2008) argue that the method used to elicit self-reported information on adherence can improve reliability. One suggestion given is that using interviewers unknown to the patient will prevent any incentive they may have in lying to an authority figure that has a stake in their treatment. Another suggestion is that by asking detailed questions about their medication taking, as opposed to a simple yes-no question, more accurate information is obtained. The data used in this thesis assessing adherence were based on self-reported information. The methods used will be described in more detail below in the description of the datasets.

Across methods of assessing adherence, most studies use binary indices of non-adherence. In reality, however, it is much more likely that there is a continuum of the degree to which patients do not adhere to their medications (Aikens, Nease et al. 2005). Non-adherence can occur at different points in time after a drug is prescribed and varies as to the duration of missed dosages. For example, Urquhart (1997) identified six categories of non-adherers: (i) those that miss a dose but then take the missed dosage soon after they were supposed to take it; (ii) those who miss very few doses; (iii) those who miss a few doses, but never more than one at a time; (iv) those who a few times a year miss more than one dosage at a time ('drug holidays'); (v) those who regularly take drug holidays; and (vi) those who take few or no doses. Weiden et al (2004) identified various degrees of partial compliance based on the maximum number of days in any gap in medication taking over a one year period and observed statistically significant increases in the rate of rehospitalisation as the maximum gap in medication increased. Donohue et al (2001) similarly used more than two categories to classify adherence, while Grunebaum et al (2001) used the continuous measure: number of days in the month prior to interview on which no medication was taken.

In the studies reviewed, the definition of what constituted non-adherence varied substantially. Some studies defined non-adherence as discontinuation of medication for one week or longer (Robinson, Woerner et al. 2002), while others classified ever missing medication as constituting non-adherence (Weiden, Kozma et al. 2004).

The reviewed literature highlighted other important inconsistencies in the methods used in assessing factors associated with non-adherence in patients taking antipsychotics. In particular, the length of time over which non-adherence was assessed differed across studies. The length of time over which adherence status was assessed in previous studies ranged from one month to five years. This is important as the length of time under study is likely to impact on the prevalence of non-adherence observed. Shorter studies may not follow patients long enough to observe the long-run medication taking behaviour of patients. Of the 43 empirical studies reviewed, only 17 (40%) assessed medication taking over a time period of one year or more.

In summary, there are a wide range of methods that can be used to assess adherence, and the choice of assessment method should be determined by the goals of the study and the relative advantages and disadvantages of the methods (Andrade, Kahler et al. 2006).

2.3 Costing methods

There are several sources of costs that result from the incidence of schizophrenia. The key cost drivers are: inpatient services, specialist community accommodation, medication, lost employment, premature mortality, family burden and public safety and concern (Knapp, Simon et al. 2002). The first three of these are examples of direct costs. That is, they are costs that are incurred for provision of health services to patients (Knapp 1996). Indirect costs are the necessary, or at least desirable (in some respect), complements to direct expenditure from local authorities and other agencies. An example of an indirect cost in the support of a patient with schizophrenia is a carer support service. Costs that are not immediately identifiable, but are measureable, such as family support, are considered hidden costs. Premature mortality, family anxiety, and public safety are examples of immeasurable costs (Knapp 1996).

While many of these costs drivers can be identified, there may be difficulties in attaching a unit cost to them. This is because they may not best equate to the money cost or price of the resources because of market distortions of prices. The appropriate measure of the cost of a service is the benefit forgone or opportunity cost of not using the resource in is best alternative use.

Another important consideration in analyses of costs is the perspective taken. Typically this will either be the perspective of the health and social care system, the public/sector/government or of the society as a whole. Health and social care costs focus on the direct costs of services. A public sector/government perspective would include health and social care costs and those indirect costs, such as the cost of benefits, paid out of the public purse. Taking a societal perspective necessitates the inclusion of all costs borne by society, including such indirect costs as informal care and lost productivity. In this thesis the health and social care system is taken in each empirical analysis. The data necessary to conduct such analyses were available in each of the datasets. Where additional data were collected allowing for estimation of public sector/government costs, the cost of lost employment or societal costs, these were estimated and analysed.

2.4 Measuring and costing psychiatric services

Beecham and Knapp (2001) identified four 'rules' for costing mental health services. These are:

1. Costs should be comprehensively measured ranging over as many service components of care packages as is relevant
2. Variations between clients and variations between facilities or areas of the country should not be overlooked
3. Assessments of the comparative performance of services should be made on a like-with-like basis
4. Cost information is more useful if it is used in conjunction with outcome data

With regards to comprehensively measuring costs, this is most effectively done at the individual level. Thus collecting service receipt or utilisation data for individual patients or clients over a specific period of time will achieve comprehensiveness.

The first step to comprehensively costing services is to describe the elements of the service (Beecham 1995). This involves collecting detailed information of the service and its

components. Following this, a unit of measurement for each service is chosen which reflects the typical unit of contact patients or clients have with the service. For example, a social worker may typically see clients in hourly appointments so the number of contact hours would be most easily estimated. The third step is then to identify and collect data on the cost implications of all service components. For example, staff time potentially includes salary, national insurance contributions and travel costs and decisions must be made as to the most appropriate ways to assign these to each unit of service provision. The final step in costing services is to estimate the unit cost of the service.

Unit cost measures should be based on long-run marginal opportunity costs (Beecham 1995). This method takes a long-term perspective on resource implications, taking into account developments in care that could be achieved by using present services more intensively. It also includes only those effects on resources that can be attributed to the service user (Knapp 1996), and reflects the additional cost attributable to providing the service to an additional patient or client. Opportunity costs take the perspective that costs incurred are forgone opportunities to spend financial resources alternatively.

The unit costs used in this thesis are estimates of long-run marginal opportunity costs at a national level, taken from an annual compendium of health and social care costs. Initially, an attempt was made to use unit costs consistent with the year in which the data from each source was collected. A later decision was taken to use the same year in two of the empirical analyses in which very similar sampling methods and questionnaires were used in order to facilitate comparisons across the results. The Unit Costs of Health and Social Care, compiled by Netten el al (2002), reported estimates of unit costs for over 70 health and social care services based on routine data, literature and ongoing research. The estimates include capital, revenue and other relevant direct or indirect costs of mental health and social care services. Revenue costs include salary, supplies, overhead costs as well as catering and domestic costs in the case of services provided in residential care settings. Because a long-term perspective is taken, the cost of creating services was also included. That is, the cost of buildings, land and equipment which constitute capital costs. Building and land costs are annuitized over 60 years (to reflect the assumed lifetime of a building) and discounted to arrive at an annual, present value cost. The compendium includes data to allow for unit costs to be specific to the area of the country in which patients reside but this information was not used here due to the complexity of applying this data for individual patients. With respect to the fourth rule of

costing psychiatric services, the focus here is on resource use, and as discussed in the introduction, there is an assumption in assessing the impact of non-adherence, that prescribed medications are clinically effective.

2.5 Potential confounding variables

The literature review of previously published empirical studies and reviews was used to identify factors to include in the modeling as potentially associated with non-adherence and as covariates in the analysis of costs. Table 1.1 in chapter 1 lists the factors assessed in previously published literature reviews for their association with non-adherence. As I am conducting secondary data analyses, the factors that could be considered were restricted to those relevant factors included in each of the datasets. Using the classification suggested by Fenton et al (1997), discussed in Chapter 1, the majority of the available and relevant data are patient-related. Little data were available on medication- or environment-related factors (e.g. intensity of treatment or therapeutic alliance) or those that related to psychodynamic considerations (e.g. degree of insight into illness). The control variables in each dataset are listed and described in the empirical chapters (3, 4 and 5) which describe the variables in more detail.

2.6 Data sources

The choice of datasets to use in the analyses was based on the extent to which relevant information was included in the dataset. The features deemed most important were that the sample was nationally representative, the data were collected relatively recently, had an adequate measure of non-adherence, included comprehensive information on health and social care service use and indices of as many as possible of the potential covariates relevant to non-adherence and service use. Additionally, longitudinal data were sought as these have the advantage of allowing for greater confidence in determining the direction of associations between variables. As secondary data were used, it was inevitable that not all of these features could be identified in a single dataset. For example, there were data that would have improved

the analyses that were not included in the datasets chosen. Also, particular variables were not categorised in a way that would be most relevant in the analysis. These and other limitations are discussed in detail in the chapters presenting the empirical analysis. Here, a brief overview of the datasets is given.

The relevant information in describing secondary data, as set out by Boslaugh (2007), are as follows:

What was the original purpose for which the data was collected?
What kind of data is it, and when and how were the data collected?
What cleaning and/or recording procedures have been applied to the data?

Given the methodological issues identified, and the desire to conduct an analysis on validated and representative data, the following sources were identified.

2.6.1 The Psychiatric Morbidity Surveys, 1993-4

The UK Psychiatric Morbidity Surveys (PMS) were cross-sectional, epidemiological surveys conducted in a range of settings. Interviews were conducted by the Social Survey Division field force of the British Office of Population Census and Surveys (now called the Office for National Statistics) between April 1993 and August 1994 (Meltzer, Gill et al. 1995; Gill, Meltzer et al. 1996; Meltzer, Gill et al. 1996). The PMS data were provided by the UK Data Archive.

The nature of schizophrenia determines that there will always be significant subgroups of people with the illness who will be in difficult-to-reach areas of society. For example, rates of schizophrenia are high in prison and homeless populations (Lamb and Lamb 1990; Singleton, Meltzer et al. 1998). These patients are rarely considered in analytical studies (Gill, Meltzer et al. 1996). A significant advantage of the PMS 1993-4 data is that a sample of homeless people was included in the data.

The aims of the 1993-4 PMS surveys are listed as:

(a) to estimate the prevalence of psychiatric morbidity according to diagnostic category among adults aged 16 to 64 years in Great Britain
(b) to identify the nature and extent of social disabilities associated with mental illness
(c) to examine the varying use of services and the receipt of care in relation to the mental illness and the associated social disabilities
(d) to investigate recent precipitating factors which are associated with mental illness
(e) to investigate the relationship between mental illness and smoking, drinking and drugs use

The assessment of non-adherence in the 1993/4 PMS was based on self-assessment by survey respondents. The assessment relates to current medications only and is based on survey responses to the questions 'Do you sometimes not take your medications even though you should?' and 'Do you sometimes take more medication/pills than the stated dose?'

Data on the frequency of use of inpatient care, outpatient care, external services (including community psychiatric nurse, occupational therapist, social worker, community psychiatrist, home help, volunteer worker), day care and sheltered employment were available from the survey.

The 1993/4 PMS includes several variables that relate to the analysis of the factors associated with non-adherence and the analysis of factors associated with costs. These are: age, sex, education, general level of health, illness severity, inpatient contact for mental health reasons in the past year, self-reported drug abuse, self-reported alcohol abuse, level of support from family or friends and familiarity with medication. The dataset also has a variable indicating if a patient is from an ethnic minority.

2.6.2 The QUATRO Study

The QUATRO study was a multi-national randomized controlled trial carried out at four centres across four European countries (Germany, Italy, the Netherlands and the UK), funded by the European Commission and coordinated from the UK. It has the advantage of following patients over time. Its main aim was to compare the effectiveness of adherence therapy with a health education control intervention (which allows for therapist time and relationship), in improving health-related quality of life for people with schizophrenia receiving treatment from general adult mental health services (Gray, Leese et al. 2006). The sample was drawn from adults receiving care from psychiatric services in each of four European cities: Amsterdam (The Netherlands), Leipzig (Germany), London (United Kingdom) and Verona (Italy). Data collection took place between June 2002 and October 2003 (Gray, Leese et al. 2006). Each sample was recruited from the patient records of senior treating clinicians at a range of local in-patient and community settings that were typical of general treatment centres in the catchment areas of each site. The inclusion criteria were that the patient must have had a clinical diagnosis of schizophrenia, must require on-going antipsychotic medication for at least one year following the baseline assessment, and must have exhibited evidence of clinical instability in the year prior to baseline (Gray, Leese et al. 2006). Clinical stability is defined as meeting one or more of the following criteria: a hospital admission on mental health grounds, a change in the type or dose of antipsychotic medication, planned or actual increased frequency of contact with mental health services, and indications of clinical instability reported by relatives, carers or the clinical team. Written, informed consent was obtained from all participants.

The study was a two-arm randomised controlled trial. Patients were randomly assigned to either receive the experimental intervention, an individual cognitive-behavioural approach which is collaborative and patient-centred, or a standard health education control intervention. The six elements that form the core of the cognitive-behavioural approach are assessment, medication problem-solving, a medication timeline, exploring ambivalence, discussing beliefs and concerns about medication, and using medication in the future (Gray, Leese et al. 2006).

Measurements were taken at baseline and after 12 months for both the intervention and control groups. Adherence to medication was based on patient responses on the Medication

Adherence Questionaire (MAQ). Positive responses on the MAQ are summed to obtain a Morisky score (Morisky, Green et al. 1986), a 5-point scale based on 4 questions relating to medication-taking behaviour. It asks patients if they ever forget to take medication, if they are careless about taking medication, if they ever stop taking medication once they feel better and if they ever stop taking medication because it made them feel worse. The Morisky score is widely used to assess adherence (Shalansky 2004; Day, Bentall et al. 2005). For the purpose of this analysis, values of 3 and 4 on the 5-point scale (0-4) were deemed as reflecting a high liklihood of non-adherence as per classifications found in the literature (Shalansky 2004).

In the QUATRO study, service use information is collected on the Client Service Receipt Inventory (CSRI) (Beecham and Knapp 1992). The CSRI collects individual patient data on demographic characteristics, accommodation and living situation, employment history and earnings, including receipt of benefits, health and social care service receipt, and the role of informal carers. This questionnaire was originally designed to be used by an interviewer with the principle carer of a person with mental health problems. The QUATRO study team choose to have the CSRI administered by non-economist researchers in a face-to-face interview with participants (Patel 2006). Due to uncertainty over the reliability of service use reports by people with mental health problems, interviewers were advised that, where full data could not be obtained from participants, they should obtain supplementary information from key workers, service providers and/or carers to ensure that the information was as complete and reliable as possible.

For use in the non-English speaking QUATRO study sites, local language versions of the CSSRI-EU were available from the EPSILON study (Chisholm, Knapp et al. 2000), which carried out a process of translation into local languages, focus groups and pilot activities to ensure face validity and semantic equivalence.

The CSRI can be used for the chosen retrospective period as it breaks down service receipt into typical units of contact. In the QUATRO study the retrospective period to which the service use data refers was three months.

2.6.3 The Psychiatric Morbidity Survey, 2000

The Psychiatric Morbidity Survey, 2000 collected information both in its own context and relating to the 1993-4 PMS studies. The positive aspects of this dataset are that it provides more recent service use data and by having a methodology largely consistent with the previous PMS data, offers a good comparison across the two studies. The difficulty is that the study sample includes individuals residing in private households only and is thus not ideal for comparison of schizophrenia patient samples. The 2000 PMS data was provided by the UK Data Archive.

The main aim of the survey was to collect data on the prevalence of mental health problems among adults aged 16 to 74 years living in private households in Great Britain (Singleton, Bumpstead et al. 2001). The topics of the 2000 PMS Household survey were similar to those in the 1993-4 surveys. The questions relating to non-adherence to medication were worded identically to those in the 1993-4 surveys. Service use data were collected for each of the following category of services: GP consultations, inpatient visits, outpatient visits, day activity services, and community care services (including community psychiatrist, community psychologist, community psychiatric nurse, social worker, home help, outreach worker).

The sample in the PMS 2000 was independent of the sample from the 1993-4 surveys. Given the likely similarity between the household samples in each, however, the PMS 2000 data would be ideal for comparing rates of non-adherence and the nature of the association between non-adherence, relevant covariates and service use. Unfortunately, in the 2000 PMS only 54 patients reported being prescribed antipsychotics at the time of the interview. This survey was used instead to assess service use and costs in another mental illness sample, patients taking antidepressants, to contrast the significance of non-adherence in relation to service use relative to the patients taking antipsychotics in the 1993-4 PMS. The service use data collected in the PMS surveys were quite similar which greatly enhances this comparison.

The six to seven year gap between the surveys is acknowledged, however. The two PMS samples were not combined because of changes in the health care system in the intervening period. For example, the number of standard dosage units of antidepressants prescribed per 1000 population increased by approximately 75% between 1993 and 2000 (Rose 2007). There

were also changes to the provision of services, including alterations to the organisation and configuration of community mental health teams, continued rebalancing of care between hospital and community settings, and growth of secure provision.

2.7 Statistical analysis

The statistical methods used in the thesis were chosen based on the features of the data. All statistical analyses were conducted using the STATA data analysis software (StataCorp 2007; STATA 10.1 2009).

2.7.1 Logistic regression

For the research question assessing factors potentially associated with non-adherence, a dichotomous index of non-adherence was used in each of the datasets. For the analyses, where the outcome involved whether a patient was adherent, a logistic regression model was fit to the data. The logistic regression model can be represented algebraically as:

$$p_i = \frac{1}{1 + e^{-B_0 - B_i X_i}}$$

where p_i represents the probability of a positive outcome in patient i, and X_i represents a column vector of observed values, for patient i, for the set of factors thought to be associated with non-adherence.

This equation can be rearranged to be expressed as:

$$p_i = \frac{e^{B_0 + B_i \overline{X}}}{1 + e^{B_0 + B_i \overline{X}}}$$

The logit transformation of p_i is:

$$g(x) = \ln\left[\frac{p_i}{1-p_i}\right] = \beta_0 + \beta_i \overline{X}$$

The function, *g(x)*, has many of the properties of a linear regression model. That is, it is linear in its parameters, may be continuous, and may take on values from -∞ to +∞.

The value then of a dichotomous outcome variable given a set of parameters, X, can be expressed as:

$y_i = p_i + \varepsilon$

where ε has a binomial distribution with mean zero and variance equal to $p_i\,[1\text{-}p_i]$.

For a dichotomous variables (say Y), either equation above for *p* gives the conditional probability of a positive event (Y=1) given values X. The conditional probability that Y=0 is thus given by 1-*p* .

The likelihood function is the product of the contribution to the likelihood function for the a pair of values (x,y):

$$l(\beta) = \prod_{i=1}^{n} p(x_i)^{y_i}[1-p(x_i)]^{1-y_i}$$

The natural log (ln) of this equation is:

$$L(\beta) = \ln[l(\beta)] = \sum_{i=1}^{n}\{y_i \ln[p(x_i)] + (1-y_i)\ln[1-p(x_i)]\}$$

To find the values of the vector of coefficients, **β**, that maximizes this equation, it is differentiated with respect to β_0 and β_1 and the resulting expressions, given below, are set equal to zero.

$$\sum_{i=1}^{n}[y_i - p(x_i)] = 0$$

and

$$\sum_{i=1}^{n} x_i[y_i - p(x_i)] = 0$$

This solution of coefficients is termed the maximum likelihood estimate.

If an independent variable in a logistic regression model is itself dichotomous, the most commonly used measure of association is the odds-ratio. If the levels of the dichotomous independent variable are 0 and 1, and the outcome variable, also dichotomous is 1 for a positive outcome and 0 otherwise, the odds-ratio represents the probability of a positive outcome among individuals with independent variable value of 1 relative to those with independent variable at value 0. For example, in the analyses to follow, if a 'positive' outcome is defined as having been non-adherent to medication and alcohol abuse is represented by 1 if the respondent has previously abused alcohol and 0 if they have not, an odds-ratio of 2 would be interpreted as those with a history of alcohol abuse being twice as likely to report non-adherence relative to those without a history of alcohol abuse.

The odds-ratio can be written as:

$$\text{OR} = \frac{p(1)/[1 - p(1)]}{p(0)/[1 - p(0)]},$$

that is, the ratio of the odds of a positive outcome for those with a value of 1 on the independent variable relative to the odds of a positive outcome for those a value of 0 on the

independent variable (Hosmer and Lemeshow 2000). Given the algebraic representation of p_i above, the formula for the odds-ratio can be reduced to:

$OR = e^{\beta_i}$.

The odds-ratio has possible values ranging from 0 to $+\infty$, with a value of 1 reflecting equal odds for each level of a dichotomous independent variable. Thus the distribution of the odds-ratio is skewed right. The sampling distribution of the maximum likelihood coefficient estimate, β_1, has a normal distribution. The endpoints of the 100(1-α)% confidence interval estimate for the odds ratio is then given by:

$\exp[\beta_1 \pm z_{1-\alpha/2} \times [\text{standard error}(\hat{\beta}_1)]$.

If an independent variable is categorical but has more than two levels, a reference category is chosen from one of the levels of the variable and odds-ratios are calculated for the remaining levels which reflect the odds of a positive outcome for that outcome level relative to the reference level. Again as an example, consider non-adherence as the 'positive' outcome and level of education as an independent variable with 3 levels – without a secondary school education, completed secondary school or completed post secondary school qualification. If 'without secondary school education' were the reference category, an odds-ratio of 2 for respondents with completed secondary school would represent a doubling of the odds of being non-adherent for those who had completed secondary school relative to those without a secondary school education. An odds-ratio of 3 for those who had completed a post-secondary school qualification would represent these individuals being three times as likely to be non-adherent as those without a secondary school education.

In the most basic case, the logit is assumed to be linear in relationship to a continuous covariate. In this case, the slope coefficient, β, is the change in the log odds for an increase of one unit on the continuous variable. For example, an odds ratio of 1.05 for the variable age means that a one year increase in age is associated with a 1.05 times the odds of a positive outcome. A more meaningful description of the association of a dichotomous outcome with a continuous independent variable may be to report the impact of a relevant or meaningful

change of units on the independent variable. It would possible then to say, for example, that 'a 10 year difference in age is associated with x times the odds of a positive outcome'.

Say the choice of a relevant or meaningful change is 'c' units. The odds ratio for a change of 'c' units is:

$OR(c) = \exp(c\beta)$

This can be estimated by replacing β with its maximum likelihood estimate $\hat{\beta}$. The endpoints of the 100(1- α)% confidence interval of OR(c) are:

$\exp[c\beta_1 \pm z_{1-\alpha/2} \text{ x c x [standard error}(\hat{\beta}_1)]$.

The link test is used to test the appropriateness of the specification of the logistic regression models (Tukey 1949). The link test regresses the outcome variable in the logistic regression on the values predicted by the model and the predicted values squared. If the squared predicted values have statistically significant explanatory power, the model is misspecified. In the case of logistic regression this would necessitate altering the specification of the independent variables as the specification of the dependent variable is set as the log likelihood function.

Several options exist for testing the goodness-of-fit of the logistic regression model. Those used in the analyses are the Pearson's chi-squared test, the Hosmer-Lemeshow test, the likelihood ratio test and the percentage of observations correctly predicted by the model (Hosmer and Lemeshow 2000). In logistic regression the fitted values are calculated for each covariate pattern and depend on the estimated probability for that covariate pattern. The Pearson's chi-squared statistic is based on the residual probability of the observed and expected values for a particular covariate pattern. This statistic is approximated by the chi-shared distribution with $J - (p+1)$ degrees of freedom, where J is the number of observations and p is the number of independent variables included in the model.

The Hosmer-Lemeshow test involves regrouping the data by ordering on the predicted probabilities and then forming a number of equally sized groups (Hosmer and Lemeshow 2000). The Hosmer-Lemeshow goodness-of-fit statistic is the Pearson chi-squared statistic for the table of observed and estimated expected frequencies for each group summed over all of the groups (Hosmer and Lemeshow 2000). This test statistic is also approximated by the chi-squared distribution with degrees of freedom equal to the number of groups minus two.

The likelihood ratio statistic is twice the difference in the log-likelihoods of two models. The significance of a particular independent variable can be tested by calculating the difference in log-likelihood of a model with the variable included and a model without the variable and multiplying this by two. The likelihood ratio test has an approximate chi-squared distribution with degrees of freedom equal to the number of independent variables in the model.

The logistic regression model fit was further assessed by looking at the percentage of observations correctly predicted by the model. That is, what percentage of patients who were non-adherent were predicted by the model to be so. There is no specific percentage that can be taken to validate the choice of model, but this statistic is useful to judge the relative performance of logistic regression models.

2.7.2 Two-part models and generalised linear models

In analysing the association between non-adherence and service use costs, specific characteristics of the distribution of costs suggest that ordinary least square methods are not appropriate. A distribution of service use typically included a significant number of zero cases, that is, patients who did not use any services during the period under study. Also, cost outcomes across a large number of patients are usually skewed to the right. That is, there are a relatively small number of patients who require very high service use and as a result have unusually high costs.

A common approach to dealing with the first of these features is to use a two-part model (Mullahy 1998). In the context of analysis of service use and costs, the first part of the model estimates whether or not a patient has any service use at all, and the second part of the model

estimates the amount of costs incurred among those patients who did use services. The first part of the model can by estimated with binary probability models - logistic or probit regression. In the analyses conducted for this thesis, when the data for a cost outcome contained a significant number of zero values, logistic regression modelling was used for the first part of a two-part model analysis.

The second part of the two-part model is a model of the costs for those patients who used services. These costs can be modelled with a linear regression model, provided that the necessary assumptions or conditions are met. That is, that the relationship between the dependent and independent variables is linear; that the residuals of the model are not correlated and have constant variance and the residuals are normally distributed (Cohen, Cohen et al. 2003). Typically, high skewed data, a common feature of cost data, will violate the condition of constant variance across the residuals (Dunn, Mirandola et al. 2003). Heteroscedasticity is the term given to non-constant variance in the residuals. Heteroscedasticity, along with the residuals not having a normal distribution, will lead to underestimates of the standard error of the parameter estimates and thus overestimation of significance levels. One approach to dealing with the skewed distribution of a regression outcome variable is to perform a transformation on the cost values – usually using the natural log: *ln(y)*. These values are then analysed with ordinary least squares regression. This method has its deficiencies, however, as the results may be biased if not appropriately retransformed (Manning and Mullahy 2001). Here part two of the model was modelled with a generalised linear model (GLM) where an extension of Park's test is applied to the raw-scale residuals from the GLM model to determine which specific GLM to use (Mullahy 1998). Algebraically, this can be represented by:

Part 1: $$\Pr(y_i>0|\ x_i) = \frac{1}{1+e^{-B_1-B_i X_i}}$$

Part 2: $$E[\ln(y_i)|\ y_i>0, x_i] = X_i\beta_i$$

where y_i is the observed cost of patient i, and X_i represents observed values, for patient i, for the set of factors thought to be associated with non-adherence.

The overall model has expected value:

$$E[y| X] = Pr(y>0|X) \times E[y|y>0,X]$$

The logit model has been described above. The generalised linear model is an extension of a linear model with three components (Blough, Madden et al. 1999). The first of these is the linear component:

$$\eta_i = X_i \beta$$

where X is a column vector of observed values for the model covariates and β is a column vector of coefficients.

The second component of the GLM model is a link function, g, which describes how the expected value of a response, y_i, is related to the linear predictor:

$$g(\mu_i) = X_i \beta$$

where $\mu_i = E(y_i)$. The log link function was used in the analysis of service use costs on account of the values being skewed to the right.

The third component is the variance function. The variance function value determines the relationship of the variance of the outcome variable across patients and their mean where each observed outcome has a probability distribution from an exponential family. This can be written as:

$$Var(y_i) = \sigma_i^2 = \Phi V(\mu_i)$$

where Φ is a constant called the dispersion parameter. The exponential family of probability distributions includes the normal (Gaussian), binomial, Poisson, gamma and the inverse Gaussian distributions.

The choice of distributional function was made based on the modified Park Test described by Manning and Mullahy (2001). The Park Test statistic is estimated using a ordinary least square with a log link where the dependent variable is:

$$\ln (y_i - \hat{y}_i)^2$$

and the explanatory variable is $\ln(\hat{y}_i)$, the natural log of the fitted value from one of the GLM specifications. Thus the model is:

$$\ln (y_i - \hat{y}_i)^2 = \lambda_0 + \lambda_1 \ln(\hat{y}_i) + v_i$$

The coefficient λ_1 is used to determine which distributional family to use. If $\lambda_1=0$ the Gaussian distribution can be used. The Poisson distribution is suggested by $\lambda_1=1$ and the gamma model is suggested if $\lambda_1=2$. And if $\lambda_1=3$ the inverse Gaussian model is suggested (Manning and Mullahy 2001).

As mentioned above, the overall estimate of an individual patient's expected service use costs was estimated by multiplying the probability of use of services from the logistic regression model by the expected costs from the GLM. The method to estimate the standard error of overall costs involves using a bootstrap algorithm. Because the distribution of the overall estimate of service use costs cannot be easily defined (as the product of a logistic regression estimate and a GLM estimate), bootstrapping simulates the distribution to arrive at an estimate of the standard error. Based on random samples drawn from the original sample, the overall estimate of service use costs is estimated. This process was repeated 1,000 times with varying random samples to create a distribution of estimates. The dispersion of these values estimates the dispersion around the estimate of costs incurred. In each analysis where two-part models were used, the bootstrap algorithm was used to derive standard errors.

2.7.3 Case types

To graphically illustrate the effect of the factors in the model, predicted costs were calculated from the models for a series of case types. An initial case was selected for each outcome

which combined the factors included in the model at arbitrarily assigned values. The overall estimate of service use costs was estimated for this case and is represented by a bar in the graph. The 95% confidence interval for this case, derived from a bootstrap algorithm when two-part models were used, were calculated and are represented by a line extending from the lower limit of the confidence interval to the upper limit of the confidence interval. Further case types, in turn, varied the value of a single factor to see the impact on predicted costs of a shift in the value for that factor. For example, an initial case type may show the predicted total service use costs for a man aged 45 on medication for over 2 year. To illustrate the effect of age, an additional prediction on the graph could show the predicted total costs for a man, aged 64 on medication for over 2 years.

2.7.4 Multiple imputation

A common problem when modelling data from a large sample is that a number of sample members will have missing data for some of the explanatory variables to be included in the model. If the individuals with missing data on one or more of the variables of interests are excluded from the modelling, the model will have less power, and the findings will be less representative of the population sampled from. There are several techniques for dealing with missing variables.

An important first step in dealing with missing values is to determine if they are a random occurrence. In many instances, missing data is not random and is related to the values of the variable under study. For example, missing data on a survey question about an individual's income is potentially related to the respondent not wanting to divulge their income if very high or very low. Where missing data are unrelated to the values of the variable or any other variable observed in the dataset it is termed 'missing completely at random (MCAR)'. Testing whether or not any of the variables with complete data is associated with an observation having missing data may be used to test the assumption of MCAR but is inconclusive as it is not possible to test that the missing values are completely random without knowing what the missing values are. For example, if it is assumed that in response to being asked their income, those with particularly high or low incomes are less likely to be willing to reveal their incomes, then the missing values on this question would relate to the values that would have

been observed had the question been answered. It is a strong assumption to assume missingness completely at random.

A less strong assumption is that missing data may be conditional on another of the explanatory variables, but not on their values or the dependent variable. This is termed 'missing at random (MAR)' (Schafer 1997). Following the previous example, missing values on an income variable would be considered MAR if those with a particular level of another explanatory variable in the model, say education, are more or less likely than others to report their income, but among those with the same level of education, the probability of reporting income is unrelated to an individual's actual income (Byrne 2001). Data is not missing at random (NMAR) if missingness is dependent on the value of the missing variable, as in the example of those with higher incomes being less willing to reveal their income.

The options for dealing with missing data depend on the assessment of its randomness. Where data is MCAR, the entire observation may be deleted (listwise deletion) or the estimation can ignore missing values but include the observation (pairwise deletion) (Scheffer 2002). Options for estimating missing values when data is MAR are to replace missing values with the mean of observed cases or use the non-missing data to predict the values of missing data using a regression model. Both these methods are mainly criticised for underestimating standard errors of estimates based on the imputed data as they do not incorporate uncertainty around the imputed values. Other methods such as weighting adjustments, where each observation is weighted according to the inverse probability of observing that observation's pattern of missing data, can produce estimates with excessive variability (Rubin 1996).

The approach taken here is to use multiple imputation. The procedure uses the observed data to estimate the missing data a multiple of times, creating equally plausible versions of the complete data set. Each of the data sets is then analysed, and the results combined using Rubin's (1987) rules for scalar estimands to produce one set of estimates and standard errors. The advantage of this method is that it preserves the variance structure of the data and incorporates uncertainty around the imputed values.

The imputation of multiple datasets was performed using the STATA program Imputation by Chained Equations (ICE) (Royston 2004; Royston 2005; Royston 2005b). The number of imputations necessary was discussed by Rubin (1996). He demonstrated that the relative

efficiency of an estimate based on the number of imputations is approximated by the equation:

$$\left(1+\frac{\gamma}{m}\right)^{-1/2}$$

where γ is the rate of missing information for the quantity being estimated, m is the number of imputations and efficiency is measured in units of standard deviations. Based on this formula, Table 2.1 below indicates efficiencies for various values of γ and m.

Table 2.1: Relative efficiencies for multiple imputation estimates based on the rate of missingness, γ, and number of imputations, m.

	γ				
M	0.1	0.3	0.5	0.7	0.9
3	98	95	93	90	88
5	99	97	95	94	92
10	100	99	98	97	96
20	100	99	99	98	98

Analysis of each multiply imputed dataset uses the same method that would be used in the absence of nonresponse. Let $\hat{\theta}_l$, W_l, l=1,…,M be M complete-data estimates and their associated variances for an estimated θ, calculated from M repeated imputations under one model (Little and Rubin 1987). The combined estimate is:

$$\bar{\theta}_M = \sum_{l=1}^{M} \frac{\hat{\theta}_l}{M}$$

There are two components to the variability associated with this estimate. The first is the average within–imputation variance, given by:

$$\overline{W}_M = \sum_{l=1}^{M} \frac{\hat{W}_l}{M}$$

The second variance component is the between-imputation component, given by:

$$B_M = \frac{\sum \left(\hat{\theta}_l - \bar{\theta}_M\right)^2}{M-1}$$

The total variability is estimated as:

$$T_M = \overline{W}_M + \frac{M+1}{M} B_M$$

where *(M+1)/M* is an adjustment for finite *M*.

Based on a Satterwaite approximation, the *t* distribution is the reference distribution for confidence interval and significance level estimates (Rubin and Schenker 1986; Rubin 1987). That is,

$$\left(\theta - \bar{\theta}_M\right) T_M^{-1/2} \sim t_v$$

With degrees of freedom, v, estimated as:

$$v = (M\text{-}1)\left[1 + \frac{1}{M+1}\frac{\overline{W}_M}{B_M}\right]^2$$

2.7.5 Endogeneity

Endogenous means 'defined within' and in economic modelling refers to reverse causality or simultaneity in cross-sectional models. Simultaneity arises when one or more of the expanatory variables in a model are jointly determined with the dependent variable. That is, an explanatory variable is determined at the same time as the dependent variable and it is not possible to determine the direction of causality. The jointly determined explanatory variable is endogenous and a model that does not account for the simultaneity will produce a biased estimate of its effect.

The problem of an endogenous independent variable is typically addressed by the instrumental variable method (Maddala 2001). Consider the standard ordinary-least-squares regression model,

$$Y_i = \beta_0 + \beta_i X_i + u$$

where Y_i is the dependent variable, β_0 is the intercept, β_i is the slope parameter for the independent variable X_i and u is the error term.

If X_i is simultaneously determined by Y_i, it can be modelled as:

$$X_i = \gamma_0 + \gamma_i Y_i + v$$

But while u is random in its effect on Y_i, it will not be random in its effect on X_i meaning that X_i and u will be correlated and X is endogenous in the model predicting Y_i (Wooldridge 2006). Inclusion of an endogenous variable in a model will result in β_i being biased and inconsistent.

Instruments are variables that are correlated with the endogenous variable but uncorrelated with the error term. Thus it is necessary to identify a variable, observed in the dataset, say z, that is correlated with the endogenous variable X_i and uncorrelated with the error term u. The condition that z is correlated with X_i can be tested by regressing X_i against z. That is modelling

$$X = \pi_0 + \pi_1 z + v .$$

Then z is correlated with X_i (i.e. Cov(z , X_i) $\neq 0$) if and only if we can reject the null hypothesis that $\pi_1 = 0$. In non-linear models such as logistic regression, a two-stage residual inclusion method is necessary for addressing endogeneity (Terza, Basu et al. 2008).

Endogeneity may also result from omitted variables and measurement error (referred to as errors-in-variables). Omitted variable bias occurs if a variable which affects the dependent variable and is correlated with one or more of the expanatory variable is not included in the regression model (Wooldridge 2006). The variation associated with the omitted variable becomes part of the error term in the standard OLS regression model. The result of omitting a key variable is that the variable(s) in the model with which it is correlated are then endogenous. Typically, omitted variable bias comes about (particularly in secondary data analysis) because omitted variables are not observed in the dataset being analysed.

Errors-in-variables arises if the true value of an explanatory variable in a regression model is unobserved but is estimated in the model by a variable that has associated with it some measurement error. Consider the model

$$y = \beta_0 + \beta_1 x_1^* + \beta_2 x_2 + u$$

where y and x_2 are observed but x_1^* is not. Let x_1 be an oberserved measurement of x_1^* such that

$$x_1 = x_1^* + e_1$$

where e_1 is the measurement error. If x_1 is used in place of x_1^* in the modelling of y and x_1 and e_1 are correlated, this model will be biased and inconsistent.

Both omitted variable bias and error-in-variables bias can be addressed with the method of instrumental variables. An alternative method for dealing with potentially omitted variables is to identify a suitable proxy variable for the unobserved variable.

In addressing potential omitted variable bias, one must also be alert to the impact of multicollinearity. Multicollinearity occurs when some or all of the explanatory variables are highly correlated. Thus in adding variables to avoid omitted variable bias, one may encounter multicollinearity if the additional variables are highly correlated with explanatory variables already included in the model. Multicollinearity may affect the estimated coefficients and their standard errors, but the model will be unbiased (Wooldridge 2006).
In the model of factors associated with service use, it may be the case that, if in accessing services an individual is reminded to be consistent in their medication taking, then non-adherence and use of services are simultaneously determined. One can also accept, for example, the possibility that the therapeutic alliance between the patient and their physician is correlated with non-adherence and if not included in the modelling, would contribute to omitted variable bias. The therapeutic alliance between the patient and their physician is unobserved in the datasets used in the analyses. Because this effect is unobserved, it will contribute to the error term in the model and the error term may then be correlated to the effect of non-adherence, thus making non-adherence endogenous.

One approach to dealing with the potential endogeneity of non-adherence in the modelling of service use would be to identify an instrumental variable for non-adherence. The difficulty posed is that due to the limited scope of the datasets analysed, it may be difficult to identify a variable that can satisfactorily be used as an instrument; that is, a variable that is correlated with non-adherence but not correlated with service use. If the basis for the endogeneity is the absence in the modelling of an omitted variable, the alternative approach would be to identify a suitable proxy measure for the ommited variable which is observed in the dataset.

2.8 Summary

To examine the nature of the association between non-adherence to medication in patients taking antipsychotics, data from the 1993/4 PMS and the QUATRO study, a randomised control trial of adherence therapy were used. As a comparison for these associations, similar analyses were conducted on a sample of patients in the PMS 2000 taking antidepressants. Within each dataset, non-adherence was assessed based on self-reported information provided

in interviews of patients. In each data source, patients were asked for detailed and thorough information on their use of health and social care services. These data were used in conjunction with estimates of the long-run marginal cost of specific services to estimate the total cost of service use from a health and social care perspective. Logistic regression models were estimated to determine the significance of factors identified in previous literature, and available in the datasets, in their association with whether a patient was adherent or not. Modelling the effect of non-adherence on service use costs involved first determining the prevalence of observations with no service use and therefore, zero costs. Where a significant number of such cases existed, two-part models were estimated. This involved modelling the presence or absence of service use in the first part of the model and using generalised linear models in determining which factors were associated with the cost of services used among those patients that did use services. In the analysis of the QUATRO data, additional terms were included to utilise the longitudinal nature of the data. Also, in each dataset, where a significant number of variables had substantial missing data, multiple imputation was used to estimate the missing values.

Chapter 3

Patterns of non-adherence with antipsychotic medication and the impact of non-adherence on costs – analyses of the 1993/4 Psychiatric Morbidity Surveys

3.1 Background

Much of the analysis of the factors associated with non-adherence and the impact of non-adherence on service use costs has been based on small surveys and medical trials data. My review of the literature, described in chapter 1, found few studies based on large, population-based data. Valenstien et al (2002) used US Veterans data to look at factors associated with non-adherence. In similar large-scale population-based studies, Cooper et al (2007) conducted a population-based study in the province of Quebec in Canada using the provincial health insurance database, and Karow et al (2007) used data from the European Schizophrenia Outpatient Health Outcomes (SOHO) study to again look at a factors associated with non-adherence. Also, Janssen et al (2006) studied inpatients with schizophrenia and other psychoses in Germany, identifying patients through hospital admissions in seven psychiatric hospitals across Germany. Becker et al (2007) identified patients based on Medicaid lists in the US state of Florida. Only the study by Becker et al looked at the role of non-adherence on service use costs.

This analysis, a secondary analysis of the 1993/4 Psychiatric Morbidity Survey data, sought to provide results based on a large, nationally representative, British sample. The Psychiatric Morbidity Surveys are cross-sectional, epidemiological surveys conducted in a range of settings throughout Great Britain. Interviews were conducted by the Social Survey Division field force of the British Office of Population Census and Surveys (OPCS; now called the Office for National Statistics) between April 1993 and August 1994 (Meltzer, Gill et al. 1995; Gill, Meltzer et al. 1996; Meltzer, Gill et al. 1996). The first part of the analysis aims to examine rates of non-adherence to antipsychotic medication, and to identify the key factors that appear to be associated with patterns of non-adherence. The second part seeks to estimate the impact of non-adherence on resource use and their associated costs.

3.2 Methods

3.2.1 The sample

The 1993-4 Psychiatric Morbidity Surveys collected data from residents of private households, persons living in institutions, and homeless persons. Each group were sampled separately. The OPCS postcode address file was the source of the sampling frame from which sectors and addresses were selected for the household sample (Meltzer, Gill et al. 1995). The sampling aimed to identify a relatively small number of people in a large number of areas. Postal sectors were the primary sampling unit, and were stratified by socio-economic group. In England and Wales postal sectors were sampled with probability proportional to the number of postal delivery points, and addresses were selected within each of these. In Scotland, the multiple occupancy count was used as the basis of probabilistic sampling within sampling sectors to identify addresses. In total, 200 postal sectors were selected. At each address, eligible individuals were given an initial questionnaire and those who reported a long-standing mental illness, use of antipsychotic medication or contact with services relating to a psychotic illness or screened positive on the CIS-R (a diagnostic instrument for neuroses) or the Psychosis Screening Questionnaire were followed up in greater detail relative to the remaining interviewees. Interviews took place between October and December 1993.

The initial step in identifying intstitutions to sample from was to obtain the names and addresses of all institutions that provide some medical and/or residential care for adults with mental illness. Institutions included in the sample included the following: establishments which accommodate mentally ill adults were categorised into residential accommodation, National Health Service (NHS) accommodation, and private hospitals, homes and clinics and unregistered accommodation (Meltzer 1993). Within the three types of registered accommodation for people with mental illness, the survey aimed to sample one in thirty of all adults in the 16 to 64 years age range. These institutions were ordered by their number of beds and a sampling fraction applied to each. No centralised list of unregistered accommodation for mentally ill adults existed from which to sample, so the study team wrote to all general managers of district health authorities and all directors of social services of health authorities to construct a list to use as a sampling frame of unregistered accommodation.

A pilot survey was conducted in 1992 to test the organisation of the survey and the interview schedules and procedures. The interviews for the main institutional survey took place between April and July in 1994.

The homeless sample included residents of hostels, residents of private sector leased and short life accommodation, adults staying in night shelters and people sleeping rough (Gill, Meltzer et al. 1996). The survey team categorised hostels specifically catering for people with mental illness as institutions to be included in the institutional sampling as opposed to the homeless sampling. Hostels were ordered by size within local authorities and a systematic equal probability sample of hostels was drawn. Those sleeping rough were sampled through their use of day centres. The survey did not attempt to sample those sleeping rough who did not use day centres. For each of the types of temporary accommodations used by the homeless, the sampling frame was stratified by size and a sample of units/addresses was systematically sampled from, after taking account of the probability of being sampled. The interviews of homeless persons took place between July and August 1994.

All patients prescribed antipsychotic medication at the time of the survey were included in the analyses. This sample may include some patients who are being treated for a mental illness other than schizophrenia, but based on evidence of the trends in the off-label prescribing of antipsychotics, at the time of the PMS 1993-1994, only a small minority of patients would be prescribed antipsychotics without having a diagnosis of schizophrenia (Hodgson and Belgamwar 2006). For consistency, interviews conducted with proxy respondents were excluded. Much of the information required in the analyses was based on reporting of personal information on medication taking and service use which, in order to be reliable and accurate, would be provided by the interviewee.

3.2.2 Variable definitions

The analyses rely on self-reported determination of non-adherence. In the dataset it was not possible to distinguish between medication not taken deliberately and occasions when patients forgot to take their medication. The assessment of non-adherence in the PMS relates to current medications only and is based on survey responses to the questions ‘Do you sometimes not take your medications even though you should?’ and ‘Do you sometimes take

more medication than the stated dose?'. Thus I sought to include not only patients who took less medication than they were prescribed, but also those who took more. In the analysis no differentiation is made between patients prescribed oral medication and those prescribed to receive depot injections. It was not possible to corroborate self-reported adherence with pill counts or physiological data in the survey. Indeed, few studies do so (Zygmunt, Olfson et al. 2002). All measures of adherence have their drawbacks, but only self-report will be feasible in a large-scale survey such as this. Because I rely on self-reported information, it is likely that patients who are unaware of mistakes they are making in their medication regime are incorrectly classified as being adherent. Thus my analyses may underestimate the prevalence of non-adherence. Also, as the analyses include only those taking antipsychotics at the time of the survey, it excludes those patients who were not on medication when interviewed because they had refused medication.

The review of previous empirical literature that analysed the relationship between non-adherence and patient- , medication- and environmental-related factors identified the following variables within the data to include in the modelling: age, sex, ethnicity, education, general level of health, illness severity, previous experience of side effects, inpatient contact for mental health reasons in the past year, self-reported drug abuse, self-reported alcohol abuse, level of support from family or friends, and familiarity with medication. These factors were analysed for their association with non-adherence and as covariates in modelling service use costs.

Data on ethnicity was collected in nine categories: White, Black–Caribbean, Black–African, Black–Other, Indian, Pakistani, Bangladeshi, Chinese and none of the above. Due to the small number of non-White respondents in each of the remaining ethnicity categories, these were combined to create a dichotomous ethnicity variable to use in the analysis. Education was classified into those with higher qualifications or A-levels, those who completed O-levels, and those with no O-level qualifications.

Levels of general health were reported by patients on a five-point scale which was collapsed to three levels: very good/good; average; and poor/very poor. Severity of neurosis was based on results from the Revised Clinical Interview Schedule (CIS-R), a standardised instrument used to assess the prevalence and severity of symptoms in minor psychiatric disorders. Although administered by non-clinicians, the CIS-R has been shown to correlate closely with

standard clinical assessments (Lewis, Pelosi et al. 1992). Support from an adult with whom the patient feels close was based on the question 'How many adults who live/are staying here with you do you feel close to?'. Medication familiarity was represented by being on medication for greater than two years. Additionally, a dummy variable was created which identified the patient's place of accommodation, so that the statistical analyses could differentiate those patients living in hospitals from those in 'other' settings (residential care homes, supervised housing, group homes and hostels).

The primary analysis uses the institutions sample only. This is because very few household respondents report that they are currently taking antipsychotics and of those that do, the rate of missing values amongst the other variables included in the analyses is high. The rate of missingness is also a problem in the homeless sample. The rates of missingness and identification of the variables most affected by missingness are given in the results section.

3.2.3 Costing service use

Data on the frequency of use of inpatient care, outpatient care, external services (including community psychiatric nurse, occupational therapist, social worker, community psychiatrist, home help, volunteer worker), day activity services (including sheltered employment) for the period of one year were available from the survey (see Table 3.1).

Data on the frequency of use of inpatient care, outpatient care and day activity centres in the three months prior to interview were obtained in the survey. The number of visits was multiplied by four to estimate annual usage. The dataset categorises inpatient stays into six categories: secure or semi-secure unit, acute psychiatric ward, rehabilitation or long-stay ward, A&E department or emergency ward, general medical ward, or other. Outpatient visits were categorised into visits to A&E department of hospital casualty department, psychiatric outpatient department, other hospital outpatient department and other outpatient or daypatient service. The questionnaire differentiated day activity services as one of community mental health centre, day activity centre, sheltered workshop or other service.

Table 3.1: Health and social care services included in analyses, PMS 1993-4

Professional services for those in hospital, clinic or nursing home	Psychiatrist/Psychotherapist Other consultant/hospital doctor Psychiatric Nurse Social worker/Counsellor Occupational Therapist Psychologist Voluntary worker
GP visits	
Hospital inpatient stays	Secure/semi-secure or special hospital unit Acute psychiatric ward Rehabilitation or long-stay ward/facility A&E department or emergency ward General medical ward
Hospital outpatient visits	A&E department Psychiatric outpatient department
Day activity services	Community mental health centre Day activity centre Sheltered workshop
External services	Community Psychiatrist Community Psychologist Community Psychiatric Nurse Community learning difficulty nurse Other nursing services Social worker Self-help/support group Home help/home care worker Outreach worker/family support

Data on whether or not respondents had visited their GP was available for the two-weeks prior to the interview or, as with other health service use, for the previous year. The advantage of the two-week estimate is that the number of visits was given; the disadvantage being that the prior two weeks do not necessarily reflect typical recent GP service use. The current analysis uses the data on GP visits in the prior year and assumes two visits for those who have visited their GP during this time period.

The best available approximations to long-run marginal opportunity costs at a national level were taken from a well-known compendium for 2001 (Netten, Rees et al. 2001). This year was chosen to be consistent with the later analysis of the 2000 Psychiatric Morbidity Survey. Qualification costs were not included in the unit costs used in this analysis. The unit costs for

each type of inpatient stay were based on daily rates and include accommodation costs. For A&E outpatient visits and community care services a cost per visit was the basis of the unit cost. Here an average length of time of one hour was assumed per visit and the unit cost relating to hourly patient contact time was used. For community mental health centre and sheltered workshop visits, the average length time of visits was estimated and an hourly unit cost applied. For day activity centre visits a sessional unit cost was applied with a session being either a morning, afternoon or evening.

The unit cost of each service used was multiplied by the total number of visits to that service to estimate the annual cost for that service. The data were then summed to estimate total costs. The analyses examined total costs, and its three main components: inpatient service costs, external service costs and the costs associated with day activity service use.

3.2.4 Statistical analyses

As described in chapter 2 on methods, multiple imputation was employed when missing data was judged to be missing at random. The primary analysis was conducted on the imputed dataset. For subsamples where missingness at random could not be assumed, two secondary analyses were performed. The variables found to be significant in their association with non-adherence in the primary analysis were compared univariately with non-adherence. These univariate comparisons were made using the Pearson's chi-squared test for categorical variables (Plackett 1983) and the Wilcoxon Rank Sum test for continuous variables (Wilcoxon 1945). Secondly, total service use costs were compared across adherence status groups using the non-parametric Wilcoxon Rank Sum test.

In the primary analysis, where there is overlap with covariates used to explain non-adherence, I hoped to determine if these factors significantly affect costs over and above their influence on non-adherence. Given that this analysis looks at cross-sectional data, it can not be ruled out that the correlation between a covariate and the indicator of non-adherence will affect the significance of the main effect of that covariate in the analysis of costs. That is, that multicollinearity may exist. Whether or not a patient had an inpatient stays in the previous year was not included as a covariate in the analyses of costs as these visits were included in the services costed.

As described in the methods section, logistic regression models were used to determine the factors associated with non-adherence. These models were assessed by the link test, the Pearson's chi-squared test, the Hosmer-Lemeshow test, the likelihood ratio test and the percentage of observations correctly predicted by the model. Generalised linear models were used to test factors for their association with costs. With respect to inpatient, external and day activity service costs a significant proportion of the study sample did not utilise these services and so a two-part model was used. Part one modelled the probability that costs are incurred, while the second part modelled the intensity of costs among those who did use the service (Mullahy 1998). The probability that costs were incurred was estimated with a logistic regression model, while estimations of the intensity of costs were modelled using GLM models. Within a GLM model a link function can be specified to allow for the estimates of the parameters to be directly derived in the linear scale, and the algorithm outlined by Manning and Mullahy (2001) was used to select the distributional form of the GLM based on an extension of the Park test.

In the modelling of the probability of service use (where included) and service use costs, the effect of institution type was included as a covariate. This effect accounted for the fact that the use of certain services was likely to be associated with institution type. For example, use of inpatient services may have been more likely for individuals who at the time of the survey were not already in long-stay hospitals.

Endogeneity is a potential problem in these models. Simultineity may arise if regular contact with services has the effect of improving adherence through health service providers reminding and encouraging patients to adhere to their medication. I considered using the experience of side-effects as an instrument for non-adherence, but the obvious difficulty is that this variable itself may by associated with use of services. The limited scope of the PMS dataset with respect to factors associated with non-adherence made no other observed variable a good choice as an instrument for non-adherence. The potential for omitted variable bias exists in that factors associated with non-adherence and service use, supported by the theoretical literature, were not found in the dataset and could therefore contribute to correlation between non-adherence and the error term in the modelling. In particular, factors relating to attitudes to and preferences for support such as the therapeutic alliance between the

patient and their physician were not assessed in the PMS surveys. I included medication familiarity in the modelling of service use costs as a proxy for this effect.

Factors achieving significance at the 0.05 level were deemed statistically significant. The analysis was performed using the STATA data analysis software (STATA 2008).

Based on the modelling results, predicted costs were derived for a hypothetical case which arbitrarily set values for the predictive variables included in the modelling. Predicted values were then estimated for variations of the hypothetical case with one value of one of the explanatory variables changed. In order to estimate the confidence intervals around these predictions, a bootstrapping algorithm, incorporating 1000 repetitions, was used. This allowed me to obtain estimates of the standard error around each of the predictions. This data was then plotted in histograms illustrating the relative impact of changes to key variables. These plots were produced using the EXCEL software (Microsoft Corporation 2003).

3.3 Results

The rate of cooperation among institutions selected for the survey was poor with just over 50% participating. Thirty-one percent of the non-participating institutions were deemed ineligible as they were either acute units and did not have permanent residents, catered for people aged 65 and over or catered for those who were mentally handicapped as opposed to mentally ill. The remainder refused to take part. Refusals were most common among private institutions, smaller hospitals and residential care homes, supported lodging, unstaffed group homes and hostels.

In the household sample, of the 12,730 individuals selected for interview, 10,108 (79%) co-operated and had an initial interview which included questions on socio-demographic characteristics, general health, the Clinical Interview Schedule – Revised and the Psychosis Screening Questionnaire. Within the homeless sample the response rate varied substantially according to the source of selecting individuals to be interviewed. Of individuals identified from hostels, 74% were interviewed; within private sector leased and short-life accommodation, interviews were completed in 44% of households selected; within

nightshelters, 79% of individuals approached did in fact provide an interview; and 68% of selected visitors to day centres for homeless people were interviewed.

The Psychiatric Morbidity Survey institutions sample consists of data on 1,191 patients. Of these, the data on 313 residents of institutions were provided by a proxy, and excluded information relevant to the analyses. Of the remaining 818 subjects, 658 persons were prescribed antipsychotic medication at the time they were surveyed. The household sample has data on 10,108 patients of which 271 were interviews of proxies. Of the remaining 9,837 there were 54 respondents who were prescribed antipsychotics at the time of the interview. The homeless sample includes 1,166 individuals (530 in hostels, 268 in private sector leased (PSL) or short life accommodation, 187 in nightshelters and 181 from day centres). Within the hostel and PSL samples, data for 50 patients were provided by proxies. Only 27 individuals in the homeless sample reported that they were currently taking antipsychotics in their interview.

Table 3.2 summarises demographic data for each sample. The institutions sample is broken down into those in hospitals and those in 'other' institutions to explore the comparability of these two groups. The samples were comparable in age and ethnicity. The household sample was balanced between the sexes whereas the other samples had more males than females. The household and homeless sample members were more educated than the patients in institutions. All of the homeless respondents report good general health while less than 30% of the household sample report this level of general health. This divergence may reflect the subjective nature of responses to questions on a patient's general health. The homeless patients were found (after screening) to have higher levels of neurosis and were more likely to report side effects with their medication and drug and alcohol abuse as compared to the other samples. The homeless sample also had been taking antipsychotics for a shorter period than the remaining patients. Patients in residential care homes, supervised housing, group homes or hostels were most likely to have been on medication for greater than 2 years. Over 50% of the homeless report non-adherence to medication as compared to approximately 30% in the household sample, 20% of those in residential care homes, supervised housing, group homes or hostels and 10% of those in hospital.

Table 3.2: Demographic characteristics of sample members currently taking antipsychotics, PMS 1993-4

	Resident in Household (n=54)	Resident in Hospital (n=304)	Resident in other institutions [1] (n=354)	Homeless (n=27)
Age: mean (SD)	46.1 (11.7)	43.0 (12.6)	44.8 (10.6)	38.4 (13.5)
Sex: % male	46.3 %	71.1 %	68.4 %	77.8%
Ethnicity: % White	94.4 %	89.5 %	95.5 %	92.6 %
Education:				
% Higher qual. or A-levels	15.1 %	11.2 %	12.4 %	16.0 %
% O-levels [2]	22.6 %	12.5 %	16.2 %	20.0 %
% No O-levels	62.3%	76.3 %	71.4 %	64.0 %
General health:				
% Good	29.6 %	50.3 %	47.7 %	100 %
% Fair	48.2 %	33.6 %	41.2 %	0 %
% Bad	22.2 %	16.1 %	11.1 %	0 %
Illness severity: mean (SD) CIS-R score [3]	12.4 (11.9)	12.9 (10.9)	10.5 (9.7)	20.1 (13.3)
Ever experienced side effects: % yes	9.3 %	6.6 %	7.9 %	14.8 %
Mental health hospital stays: % yes	16.7 %	12.8 %	17.8 %	14.8 %
Drug abuse: % yes	9.3 %	7.2 %	9.3 %	29.6 %
Alcohol abuse: % yes	0 %	6.1 %	6.7 %	22.2 %
Lives with adult with whom feels close: % yes	85.7 %	55.7 %	66.2 %	100 %
Greater than 2 years on medications: % yes	64.7 %	52.8 %	78.6 %	34.8 %
Self-reported non-adherence	18 (33.3%)	34 (11.2%)	75 (21.2%)	14 (51.9%)

Overall 220 individuals (29.8% of the sample) had data missing on one or more of the variables included in the analyses. The prevalence of missing values was particularly a problem in the homeless sample. None of these respondents had complete data on the variables of interest. Within the homeless sample (n=27), 11 (40.7%) were missing one variable, 7 (25.9%) were missing two variables and 9 (33.3%) were missing three or more. Age, health status, CIS-R score and living or staying with an adult with whom they feel close

[1] Residential care home, ordinary housing with a degree of protection, supervised ordinary housing, group home or hostel.

[2] O-level were a British exam taken by students at age 16. This exam was replaced by the GCSE exam. In the PMS, achievement of O-Level equivalent qualifications constituted O-level passes of Grades A-C, GCSE passes of Grades A-C or National Vocational Qualifications level 2.

[3] The Revised Clinical Interview Schedule (CIS-R) is used to assess minor psychiatric disorder. Higher scores indicate greater prevalence/severity of neurosis.

were the variables least frequently answered by homeless respondents. Only 8 (29.6%) of the homeless sample reported their age and only 13 (48.1%) reported their general health status. Of note, all homeless respondents who responded to the question on their general health status reported very good or good health. This suggests a potential bias towards not responding to this question if the answer did not put the respondent in a favourable light. Similarly, the 19 (70.4%) of the homeless sample who responded to the question regarding whether or not they live or stay with an adult with whom they feel close all reported having such social support.

Within the household sample 33 of 54 respondents (61.1%) had compete data on the variables to be included in the analyses, 19 (35.2%) were missing one variable only, while 2 (3.7%) were missing two variables. The variable that asked whether or not the patient lived or was staying with an adult with whom they felt close was missing for 35% of the sample. Of those that did respond to the question on social support, 85.7% report living with an adult with whom they feel close.

Within the sample of respondents resident in institutions, 486 of 658 (73.9%) had complete data. One hundred and eighteen (17.9%) were missing one variable only, 35 (5.3%) were missing two variables, 16 (2.4%) had 3 missing values, 3 (0.5%) had 4 missing values. The variables with the highest number of missing values were length of time on medication (12.8% missing), whether or not they lived or stayed with an adult with whom they felt close (12.6% missing) and alcohol use (5.3% missing). The following variables had no missing values: non-adherence, experience of side effects, ethnicity, sex, age, inpatient mental health contact and type of residence. Within the homeless sample, 11 of the 27 (40.7%) patients had missing values for one variable to be included in the analysis. Seven patients (25.9%) had missing values for two variables and 9 (33.3%) had missing values for three or more variables. Data on general health was missing for two-thirds of the homeless sample and age was not reported by 19 (70.4%) of the sample.

Due to the apparent association between the missingness on questions relating to health status and social support and the observed values on these items, missingness at random, required for multiple imputation, cannot be assumed within the homeless sample. It is unclear as to whether or not a similar problem exists with the question on social support when asked within the household population. Given the small number of observations contributed by the household sample and the concern about the missing at random assumption, the decision was

taken to restrict the primary analysis to the institutions sample only. Within the institutions sample missing values are observed on the social support and length of time on medication questions, but the distribution of observed values does not suggest a bias towards non-response being associated with a particular response option.

The overall rate of self-reported non-adherence amongst the institutions sample was 16.7%. This rate differed between patients resident in hospitals (11.2%) and those living in residential care homes, group homes or hostels (21.2%). This range is somewhat lower than reports in the literature (Battaglia 2001; Conley and Kelly 2001), probably a consequence of focussing on an institutions sample where patients may receive support, encouragement and/or incentives to adhere to medication.

The logistic regression analysis identified significant associations between non-adherence and the following factors: residence in a residential care home, supervised housing, group home or hostel, having higher qualifications or A-levels, having had a mental health hospital stay in the previous year, having previously experienced side effects, and reporting alcohol abuse (see Table 3.3). Also, the probability of non-adherence increased as CIS-R scores increased (reflecting greater prevalence and/or severity of symptoms of neurosis) and decreased as the age of patients increased.

Significantly, those people resident in non-hospital institutions were over twice as likely to be non-adherent as people resident in hospital. Having higher qualifications or A-levels approximately doubles the predicted probability of non-adherence, as does having had a mental hospital stay in the previous year. The odds of not adhering with current medication were 3.2 times greater for those who have previously experienced side effects with antipsychotic medication compared to those who had not. Those who report alcohol abuse were three times as likely to be non-adherent as those who did not report it.

The model diagnostics reported are the average values across the five imputed datasets. The link test p-value (0.203) of the square of the predicted value suggests that the model is not misspecified. The Pearson's and Hosmer and Lemeshow chi-squared p-values (0.0659 and 0.2168 respectively) were not significant, indicating acceptable goodness of fit, as did the significance of the likelihood ratio chi-squared test. The percentage of observations correctly predicted by the model was 70.9%.

Table 3.3: Results of logistic regression model on factors associated with non-adherence, PMS 1993-4 Institutions sample

Variables	N=658	
	Odds Ratio	95% CI
Resident in 'other' institution [1](n=354)… …relative to resident in hospital (n=304)	2.43***	1.46, 12.34
Age (5 year increase in age)	0.85***	0.76, 0.96
Male (n=458)… …relative to Female (n=200)	0.84	0.50, 1.41
Higher qualifications or A-levels (n=76)… O-level [2] (n=102)… …relative to below O-level qualifications (n=480)	2.42*** 0.94	1.29, 4.55 0.48, 1.83
Average general health (n=250)… Poor general health (n=87)… …relative to good general health (n=321)	1.17 0.81	0.71, 1.93 0.37, 1.77
Non-White (n=48)… …relative to White (n=610)	1.39	0.61, 3.19
Prevalence/severity of neurosis: CIS-R score [3] (five unit increase)	1.18***	1.05, 1.33
Had a hospital stay for a mental, nervous or emotional problem (n=102)… …relative to not having had hospital stay for a mental, nervous or emotional problem (n=556)	1.89**	1.08, 3.31
Two or more years on medication (n=439)… …relative to less than 2 years on medication (n=219)	1.29	0.73, 2.28
Experienced side effects or worries about side effects (n=48)… …relative to having not experienced or worried about side effects (n=610)	3.19***	1.60, 6.40
Lives with adult with whom feels close (n=403)… …relative to does not live with adult with whom feels close (n=255)	0.93	0.56, 1.54
Reports moderate or high alcohol dependency (n=42)… …relative to no alcohol dependency (n=616)	3.08***	1.39, 6.85
Reports illegal drug use (n=55)… …relative to non drug users (n=603)	1.29	0.62, 2.71
Link test p-value	0.203	
Pearson's chi-sqpared test p-value	0.0659	
Hosmer-Lemeshow chi-squared test p-value	0.2168	
Likelihood ratio chi-squared p-value	<0.0001	
Percent correctly classified	70.85%	

* $p \leq 0.10$; ** $p \leq 0.05$; *** $p \leq 0.01$

[1] residential care homes/supervised housing/group homes/hostels

[2] O-level were a British exam taken by students at age 16. This exam was replaced by the GCSE exam. In the PMS, achievement of O-Level equivalent qualifications constituted O-level passes of Grades A-C, GCSE passes of Grades A-C or National Vocational Qualifications level 2.

[3] The Revised Clinical Interview Schedule (CIS-R) is used to assess minor neurotic psychiatric disorder. Higher scores indicate greater prevalence/severity of symptoms.

In the analysis of resource use and resource use costs, initially individual services were considered. Those services that were most often used and those that incurred the greatest costs were analysed individually. These services were inpatient, external and day activity services (see Table 3.4).

Table 3.4: Distribution of costs by service type, PMS 1993-4 Institutions sample

	N	Mean	Median	Standard deviation	Interquartile range
Inpatient costs	151	32,627	26,146	15,083	23,860 – 33,923
Outpatient costs	159	1,339	512	1,838	256 – 1,536
GP costs	85	483	442	147	442 - 442
External service costs	251	2,705	1,617	3,282	356 – 3,109
Day activity service costs	232	4,645	5,616	3,159	432 – 5,616
(Sheltered) work costs	41	7,983	5,284	3,254	5,284 – 11,512
Total costs	657	34,003	34,413	21,224	14,130 – 48,180

3.3.1 Inpatient services

A total of 151 patients (23.0% of sample) reported having an inpatient stay in the past year. Of those who had an inpatient stay, mean inpatient costs were £32,630. A logistic regression model of whether or not inpatient services were used found statistically significant associations between use of inpatient services and living in a residential care home, supervised housing, group home or hostel, being from an ethnic minority and having been prescribed an antipsychotic medication for less than two years (see Table 3.5). Ethnic minority patients were two and a half times as likely to have used inpatient services. Those who live in a residential care home, supervised housing, group home or hostel were over one and a half times as likely to report use of inpatient services as compared to hospital residents, as were those that were on medication for less than two years as compared to those on medication for two or more years. The association between use of inpatient services and non-adherence to medication approached statistical significance ($p=0.059$), with those non-adherent being over one and a half times as likely to have used inpatient services. Similarly,

Table 3.5: Results of logistic regression model on factors associated with having had an inpatient stay, PMS 1993-4 Institutions sample

Independent variables	N=658	
	Odds Ratio (of using services)	95% CI
Resident in 'other' [2] institution (n=354)… …relative to resident in hospital (n=304)	1.64**	1.09, 2.49
Age (5 year increase in age)	0.93	0.84, 1.02
Male (n=458)… …relative to Female (n=200)	0.70	0.46, 1.07
Higher qualifications or A-levels (n=76)…	1.44	0.79, 2.60
O-levels (n=102)… …relative to below O-level qualifications (n=480)	1.02	0.59, 1.79
Non-White (n=48)… …relative to White (n=610)	2.46**	1.24, 4.85
Average general health (n=250)…	0.91	0.60, 1.38
Poor general health (n=87)… …relative to good general health (n=321)	0.71	0.37, 1.38
Prevalence/severity of neurosis: CIS-R score [3] (five unit increase)	1.02	0.93, 1.14
Non-adherent (n=109)… …relative to adherent (n=549)	1.61*	0.98, 2.63
Lives with adult with whom feels close (n=403)… …relative to does not live with adult with whom feels close (n=255)	1.55*	0.97, 2.45
Reports illegal drug use (n=55)… …relative to non drug users (n=603)	1.35	0.70, 2.59
Reports moderate or high alcohol dependence (n=42)… …relative to no alcohol dependence (n=616)	1.88*	0.90, 3.93
Two or more years on medication (n=439)… …relative to less than 2 years on medication (n=219)	0.56**	0.35, 0.90
Link test p-value	0.714	
Pearson's chi-sqpared test p-value	0.3304	
Hosmer-Lemeshow chi-squared test p-value	0.6646	
Likelihood ration chi-squared p-value	<0.0001	
Percent correctly classified	65.59%	

* $p \leq 0.10$; ** $p \leq 0.05$; *** $p \leq 0.01$

[1] residential care homes/supervised housing/group homes/hostels

[2] The Revised Clinical Interview Schedule (CIS-R) is used to assess minor neurotic psychiatric disorder. Higher scores indicate greater prevalence/severity of symptoms.

the effect of living with an adult with whom the respondent feels close approached statistical significance with social support positively associated with having had an inpatient visit.

The goodness-of-fit tests for this model were as follows: the link test p-value (0.714) of the square of the predicted value suggests that the model is not misspecified. The Pearson's and Hosmer and Lemeshow chi-squared p-values (0.3304 and 0.6646 respectively) were not significant, indicating acceptable goodness of fit. The significance of the likelihood ratio chi-squared test also suggested the model fits the data well. The percentage of observations correctly predicted by the model was 65.6%.

A GLM model with a log link function and a gamma distribution was fitted to inpatient costs. Among those using inpatient services, the only factor found to approach a statistically significant association with inpatient costs was ethnicity (see Table 3.6). Non-White patients reported greater costs than White patients. This observed association, however, was based on a small sample of Non-White patients (n=18). Estimates of inpatient costs for a range of case types appear in Figure 3.1. The base case was of a man, age 45, White, with no O-levels, good general health, resident in hospital, who adheres to his antipsychotic medication, has a CIS-R score of 11, does not report drug or alcohol abuse, who lives with an adult with whom he feels close and has been on medication for over 2 years. Changing the characteristics of this case illustrates the relative impact of significant factors.

Ethnicity clearly had a major effect on in-patient costs: non-Whites were predicted to cost approximately £6,600 more per annum than the base case type. Patients reporting non-adherence were predicted to have excess inpatient costs of approximately £2,500 per year above the base case type.

Table 3.6: Generalised linear model on factors associated with inpatient costs, PMS 1993-4 Institutions sample

Independent variables	N=151	
	Coefficient	95% CI
Resident in 'other' [1] institution (n=91)… …relative to resident in hospital (n=60)	-0.095	-0.24, 0.051
Age	0.0020	-0.0048, 0.0089
Male (n=99)… …relative to Female (n=52)	0.019	-0.13, 0.17
Higher qualifications or A-levels (n=24)… O-levels (n=28)… …relative to below O-level qualifications (n=99)	-0.019 0.14	-0.22, 0.18 -0.076, 0.35
Non-White (n=18)… …relative to White (n=133)	0.23*	-0.028, 0.50
Average general health (n=58)… Poor general health (n=17)… …relative to good general health (n=76)	0.044 0.071	-0.10, 0.19 -0.20, 0.34
CIS-R score [2]	-0.0044	-0.010, 0.0015
Non-adherent (n=39)… …relative to adherent (n=112)	0.079	-0.097, 0.26
Lives with adult with whom feels close (n=101)... …relative to does not live with adult with whom feels close (n=50)	0.082	-0.069, 0.23
Reports illegal drug use (n=20)… …relative to non drug users (n=131)	-0.060	-0.27, 0.15
Reports moderate or high alcohol dependence (n=15)... …relative to no alcohol dependence (n=136)	0.074	-0.22, 0.37
Two or more years on medication (n=87)… …relative to less than two years on medication (n=64)	-0.064	-0.22, 0.096
Constant	10.29***	9.90, 10.67
Link function	Log	
Distributional family	Gamma	

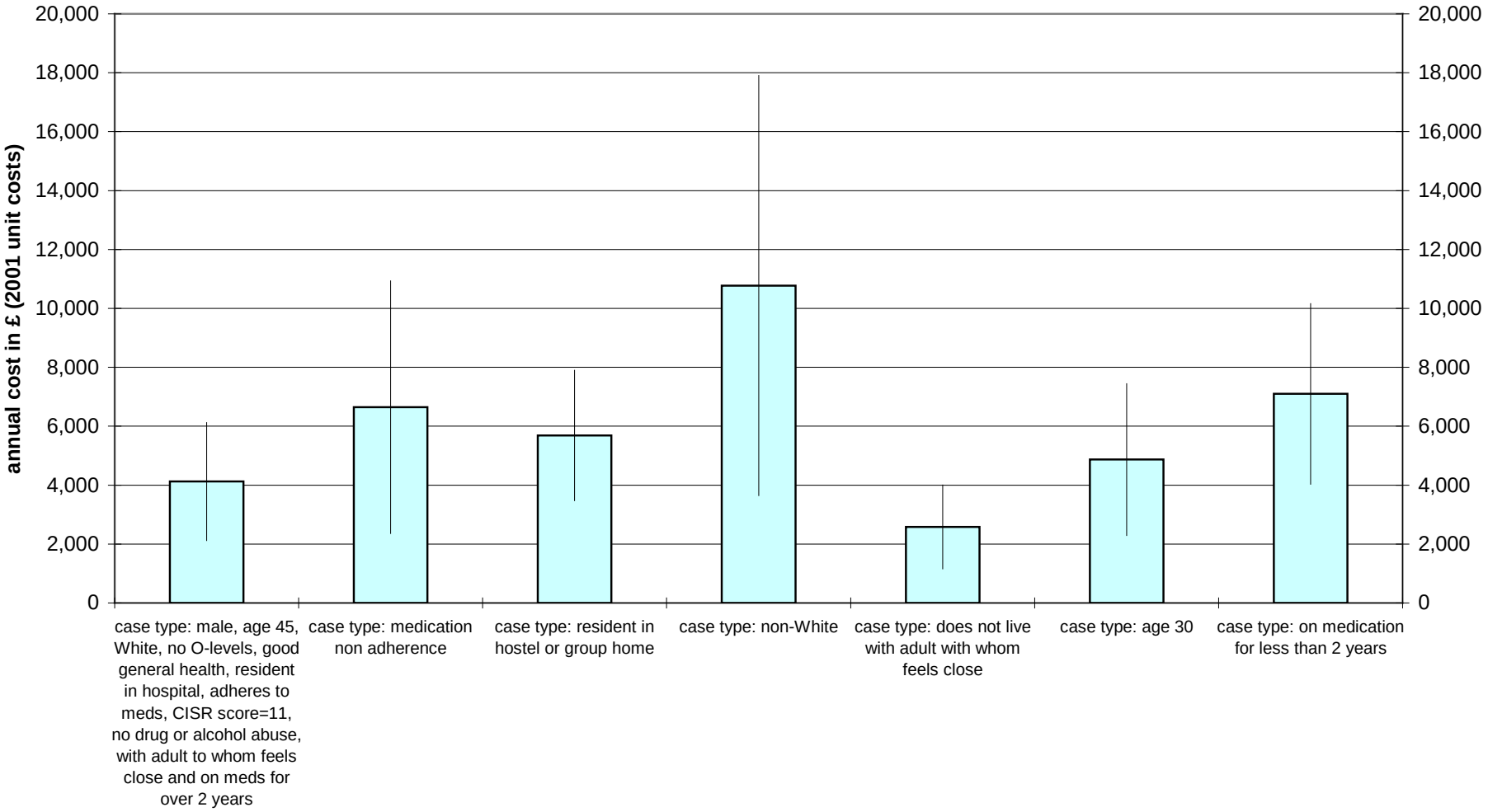
* p≤0.10; ** p≤0.05; *** p≤0.01

[1] residential care homes/supervised housing/group homes/hostels

[2] The Revised Clinical Interview Schedule (CIS-R) is used to assess minor neurotic psychiatric disorder. Higher scores indicate greater prevalence/severity of symptoms.

Figure 3.1

Predicted cost of inpatient visits, PMS 1993-4 Institutions sample



3.3.2 External services

External services include visits by a community psychiatric nurse, occupational therapist, social worker, community psychiatrist, home help or volunteer worker. The mean annual cost of external services among those who used this service was estimated at £2,705 per annum and 251 patients used these services. There was no reported use of external services by hospital residents so the dummy variable representing the effect of being in a residential care home, supervised housing, group home or hostel was excluded from the model.

Use of external services was significantly associated with non-adherence to medication, ethnicity, the CIS-R score and length of time on medication (see table 3.7). Patients who were non-adherent or were on medication for two or more years were over two and a half times more likely to use external services as compared to adherent patients and those on medication for less than two years, respectively. Non-Whites patients were significantly less likely to use external services as compared to White patients. Increases in the severity of neurosis were associated with a lower likelihood of external service use.

The square of the predicted value estimated in the link test had a p-value of 0.787 which suggests that the model was not misspecified. The Pearson's and Hosmer and Lemeshow chi-squared p-values (0.3833 and 0.6381 respectively) were not significant indicating acceptable goodness of fit, as did the significance of the likelihood ratio chi-squared test ($p<0.0001$). The percentage of observations correctly predicted by the model was 62.9%.

Table 3.7: Factors associated with use of external services [1], PMS 1993-4 Institutions sample

Independent variables	N = 658	
	Odds Ratio (of using services)	95% CI
Age (5 year increase in age)	0.94	0.86, 1.02
Male (n=458)… …relative to Female (n=200)	1.002	0.69, 1.46
Higher qualifications or A-levels (n=76)…	1.39	0.81, 2.38
O-levels (n=102)… …relative to below O-level qualifications (n=480)	1.35	0.82, 2.23
Non-White (n=48)… …relative to White (n=610)	0.48**	0.23, 1.01
Average general health (n=250)…	1.37*	0.94, 2.00
Poor general health (n=87)… …relative to good general health (n=321)	1.32	0.74, 2.34
Prevalence/severity of neurosis: CIS-R score [2] (five unit increase)	0.90**	0.81, 0.99
Non-adherent (n=109)… …relative to adherent (n=549)	2.66***	1.67, 4.23
Lives with adult with whom feels close (n=403)… …relative to does not live with adult with whom feels close (n=255)	1.17	0.79, 1.72
Reports illegal drug use (n=55)… …relative to non drug users (n=603)	1.40	0.74, 2.65
Reports moderate or high alcohol dependence (n=42)… …relative to no alcohol dependence (n=616)	1.50	0.73, 3.07
Two or more years on medication (n=439)… …relative to less than 2 years on medication (n=219)	2.86***	1.89, 4.31
Link test p-value	0.787	
Pearson's chi-sqpared test p-value	0.3833	
Hosmer-Lemeshow chi-squared test p-value	0.6381	
Likelihood ration chi-squared p-value	<0.0001	
Percent correctly classified	62.86%	

* $p \leq 0.10$; ** $p \leq 0.05$; *** $p \leq 0.01$

[1] External services include visits by a community psychiatric nurse, occupational therapist, social worker, community psychiatrist, home help or volunteer worker.
[2] The Revised Clinical Interview Schedule (CIS-R) is used to assess minor neurotic psychiatric disorder. Higher scores indicate greater prevalence/severity of symptoms.

Analysis of the factors associated with the cost of external services was based on the 251 patients who had used these services in the past 12 months. A GLM model using a log link function and gamma distribution was fitted to the data (see Table 3.8). Patients who reported drug use incurred significantly lower costs if they accessed external services as compared to those who did not report drug use. There is also a trend for having been on medication for two or more years having an association with increased external service use costs (p=0.096). Even though non-adherence increased the likelihood of use of external services, the volume of use was lower, other things being equal. Indeed the product of probability and intensity of use suggested that non-adherence increased external service use costs, while costs were substantially lower for patients on medication for less than two years (see Figure 3.2) relative to the base case. Being of average general health (as compared to good health) had the greatest impact on increasing the predicted costs of external services.

3.3.3 Day activity services

The estimated mean day care costs among users of this service were £4,645 per annum. A total of 232 patients (35.3% of sample) reported having used day activity services during the recall period. A logistic regression model of whether or not day activity services were used found statistically significant associations between use of these services and living in a residential care home, supervised housing, group home or hostel, age, self-reported health status and length of time on medication (see Table 3.9). Those who lived in a residential care home, supervised housing, group home or hostel were four times as likely to have used day care services as compared to hospital residents. Each five-year increase in age was associated with a 10% reduction in the odds of using day care services and those reporting poor health were 60% less likely to use these services as compared to those who report good health. Additionally, having been prescribed antipsychotics for two or more years was associated with 1.7 times the odds of using day care services as compared to those patients who had been prescribed antipsychotics for less than two years. The association between use of day activity services and non-adherence to medication was not statistically significant (p=0.333).

Table 3.8: Factors associated with costs of external services [1], PMS 1993-4 Institutions sample

Independent variables	N=251	
	Coefficient	95% CI
Age	-0.0026	-0.017, 0.11
Male (n=176)… …relative to Female (n=75)	0.21	-0.09, 0.51
Higher qualifications or A-levels (n=35)… O-levels (n=42)… …relative to below O-level qualifications (n=174)	-0.16 0.32	-0.55, 0.23 -0.078, 0.72
Non-White (n=12)… …relative to White (n=239)	0.11	-0.55, 0.77
Average general health (n=107)… Poor general health (n=30)… …relative to good general health (n=114)	0.16 -0.25	-0.15, 0.47 -0.65, 0.16
CIS-R score [2]	0.0042	-0.012, 0.020
Non-adherent (n=64)… …relative to adherent (n=187)	-0.16	-0.49, 0.18
Lives with adult with whom feels close (n=164)... …relative to does not live with adult with whom feels close (n=87)	0.12	-0.17, 0.41
Reports illegal drug use (n=28)… …relative to non drug users (n=223)	-0.44**	-0.85, -0.026
Reports moderate or high alcohol dependence (n=23)... …relative to no alcohol dependence (n=228)	-0.15	-0.60, 0.30
Two or more years on medication (n=199)… …relative to less than two years on medication (n=52)	0.32*	-0.058, 0.71
Constant	7.48***	6.71, 8.25
Link function	Log	
Distributional family	Gaussian	

* p≤0.10; ** p≤0.05; *** p≤0.01

[1] External services include visits by a community psychiatric nurse, occupational therapist, social worker, community psychiatrist, home help or volunteer worker.
[2] The Revised Clinical Interview Schedule (CIS-R) is used to assess minor neurotic psychiatric disorder. Higher scores indicate greater prevalence/severity of symptoms.

Figure 3.2 **Predicted cost of external services, PMS 1993-4 Institutions sample**

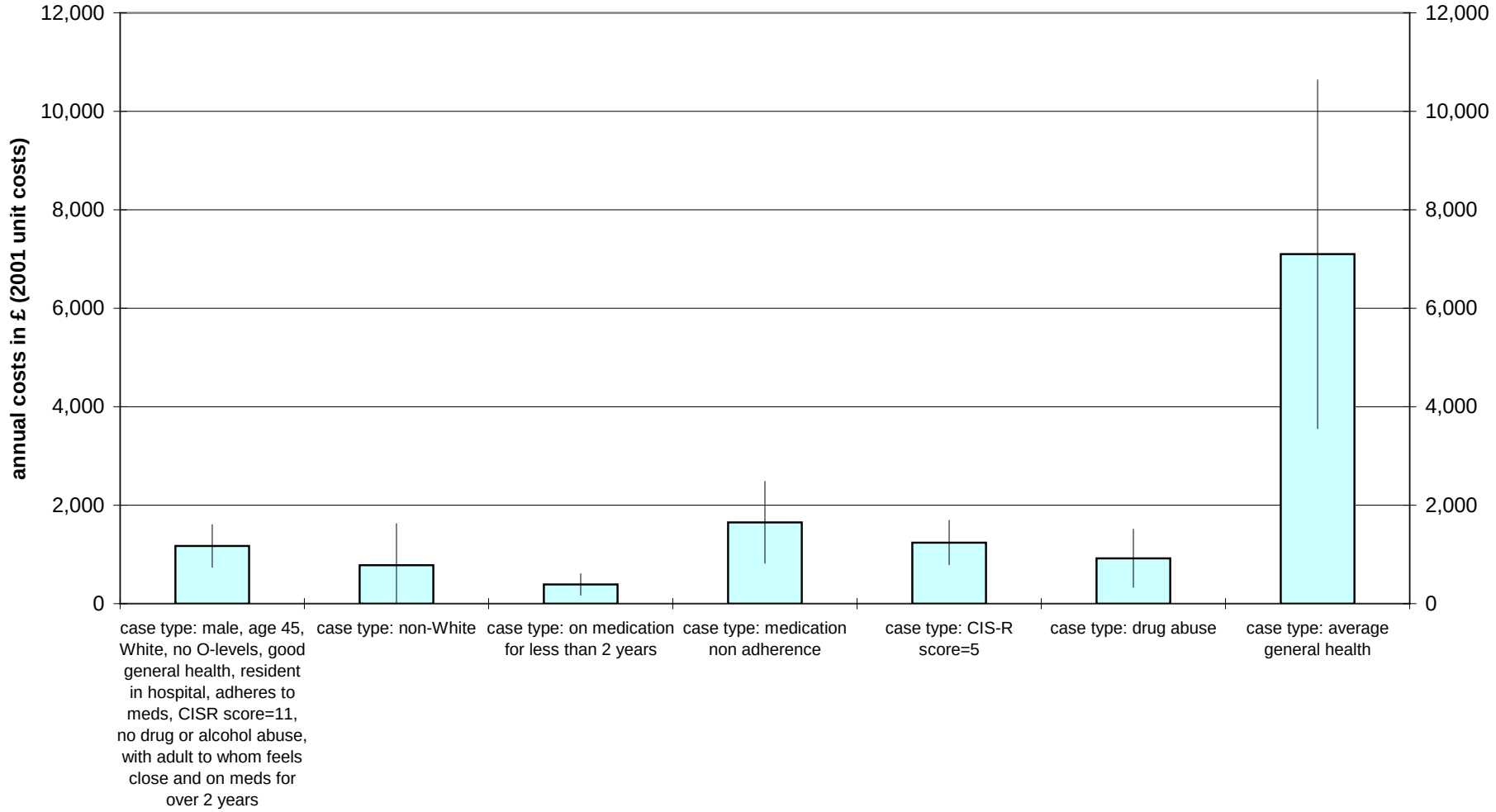


Table 3.9: Factors associated with use of day activity services [1], PMS 1993-4 Institutions sample

Independent variables	N = 658	
	Odds Ratio (of using services)	95% CI
Resident in 'other' [2] institution (n=354)… …relative to resident in hospital (n=304)	4.05***	2.76, 5.95
Age (5 year increase in age)	0.91**	0.83, 0.99
Male (n=458)… …relative to Female (n=200)	1.19	0.80, 1.76
Higher qualifications or A-levels (n=76)…	1.15	0.67, 1.98
O-levels (n=102)… …relative to below O-level qualifications (n=480)	1.18	0.70, 1.97
Non-White (n=48)… …relative to White (n=610)	0.82	0.39, 1.70
Average general health (n=250)…	0.74	0.51, 1.08
Poor general health (n=87)… …relative to good general health (n=321)	0.40***	0.21, 0.78
Prevalence/severity of neurosis: CIS-R score [3] (five unit increase)	1.0056	0.91, 1.11
Non-adherent (n=109)… …relative to adherent (n=549)	0.79	0.48, 1.28
Lives with adult with whom feels close (n=403)… …relative to does not live with adult with whom feels close (n=255)	1.08	0.74, 1.58
Reports illegal drug use (n=55)… …relative to non drug users (n=603)	1.12	0.59, 2.12
Reports moderate or high alcohol dependence (n=42)… …relative to no alcohol dependence (n=616)	1.70	0.83, 3.48
Two or more years on medication (n=439)… …relative to less than 2 years on medication (n=219)	1.70**	1.10, 2.62
Link test p-value	0.152	
Pearson's chi-squared test p-value	0.4436	
Hosmer-Lemeshow chi-squared test p-value	0.3924	
Likelihood ration chi-squared p-value	<0.0001	
Percent correctly classified	65.02%	

* p≤0.10; ** p≤0.05; *** p≤0.01

[1] Day activity services include visits to a community mental health centre, day activity centre or sheltered workshop.
[2] residential care homes/supervised housing/group homes/hostels
[3] The Revised Clinical Interview Schedule (CIS-R) is used to assess minor neurotic psychiatric disorder. Higher scores indicate greater prevalence/severity of symptoms.

The link test p-value (0.152) suggested that the model was satisfactorily specified. The Pearson's and Hosmer and Lemeshow chi-squared p-values (0.4436 and 0.3924 respectively) were not significant indicating acceptable goodness of fit. The significance of the likelihood ratio chi-squared test ($p<0.0001$) also suggested acceptable goodness of fit. The percentage of observations correctly predicted by the model was 65.0%.

A GLM model with a log link function and a Gaussian distribution was fitted to day activity service use costs (see Table 3.10). Among those using day care services, none of the factors included in the model were found to be associated with day activity service use costs. Figure 3.3 presents the predicted cost of day activity services combining the logistic regression and GLM results. Compared to the base case type, the effects of living in an institution other than a hospital and being younger in age had the greatest impact on increasing the cost of day activity services.

3.3.4 Total health and social care costs

The final model examined factors associated with the total costs of all health and social care services. The mean observed total cost was £33,795 per annum. A single GLM model was used, as opposed to a two-part model, because all but one patient had used at least one service and therefore incurred costs. A log link function and a Gaussian distribution were used in the GLM (see Table 3.11). Type of residence was found to be statistically significant. People living in residential care homes, supervised housing, group homes or hostels incurred significantly lower total costs compared to hospital residents. There was a trend for those patients who reported non-adherence to have greater total costs than those who adhered to their antipsychotic medication

Table 3.10: Factors associated with costs of day activity services [1], PMS 1993-4 Institutions sample

Independent variables	N=232	
	Coefficient	95% CI
Resident in 'other' [2] institution (n=175)… …relative to resident in hospital (n=57)	0.085	-0.17, 0.34
Age	-0.0069	-0.020, 0.0058
Male (n=166)… …relative to Female (n=66)	0.12	-0.090, 0.34
Higher qualifications or A-levels (n=29)… O-levels (n=38)… …relative to below O-level qualifications (n=165)	0.14 -0.071	-0.11, 0.39 -0.30, 0.16
Non-White (n=12)… …relative to White (n=220)	0.060	-0.27, 0.39
Average general health (n=89)… Poor general health (n=18)… …relative to good general health (n=125)	-0.0069 -0.014	-0.26, 0.25 -0.44, 0.41
CIS-R score [3]	0.00038	-0.011, 0.012
Non-adherent (n=42)… …relative to adherent (n=190)	0.015	-0.24, 0.27
Lives with adult with whom feels close (n=151)... …relative to does not live with adult with whom feels close (n=81)	0.078	-0.17, 0.33
Reports illegal drug use (n=24)… …relative to non drug users (n=208)	0.13	-0.17, 0.43
Reports moderate or high alcohol dependence (n=19)... …relative to no alcohol dependence (n=213)	0.16	-0.21, 0.53
Two or more years on medication (n=181)… …relative to less than two years on medication (n=51)	0.18	-0.058, 0.41
Constant	8.35***	7.73, 8.97
Link function	Log	
Distributional family	Gaussian	

* p≤0.10; ** p≤0.05; *** p≤0.01

[1] Day activity services include visits to a community mental health centre, day activity centre or sheltered workshop.
[2] residential care homes/supervised housing/group homes/hostels
[3] The Revised Clinical Interview Schedule (CIS-R) is used to assess minor neurotic psychiatric disorder. Higher scores indicate greater prevalence/severity of symptoms.

Figure 3.3

Predicted cost of day activity services, PMS 1993-4 Institutions sample

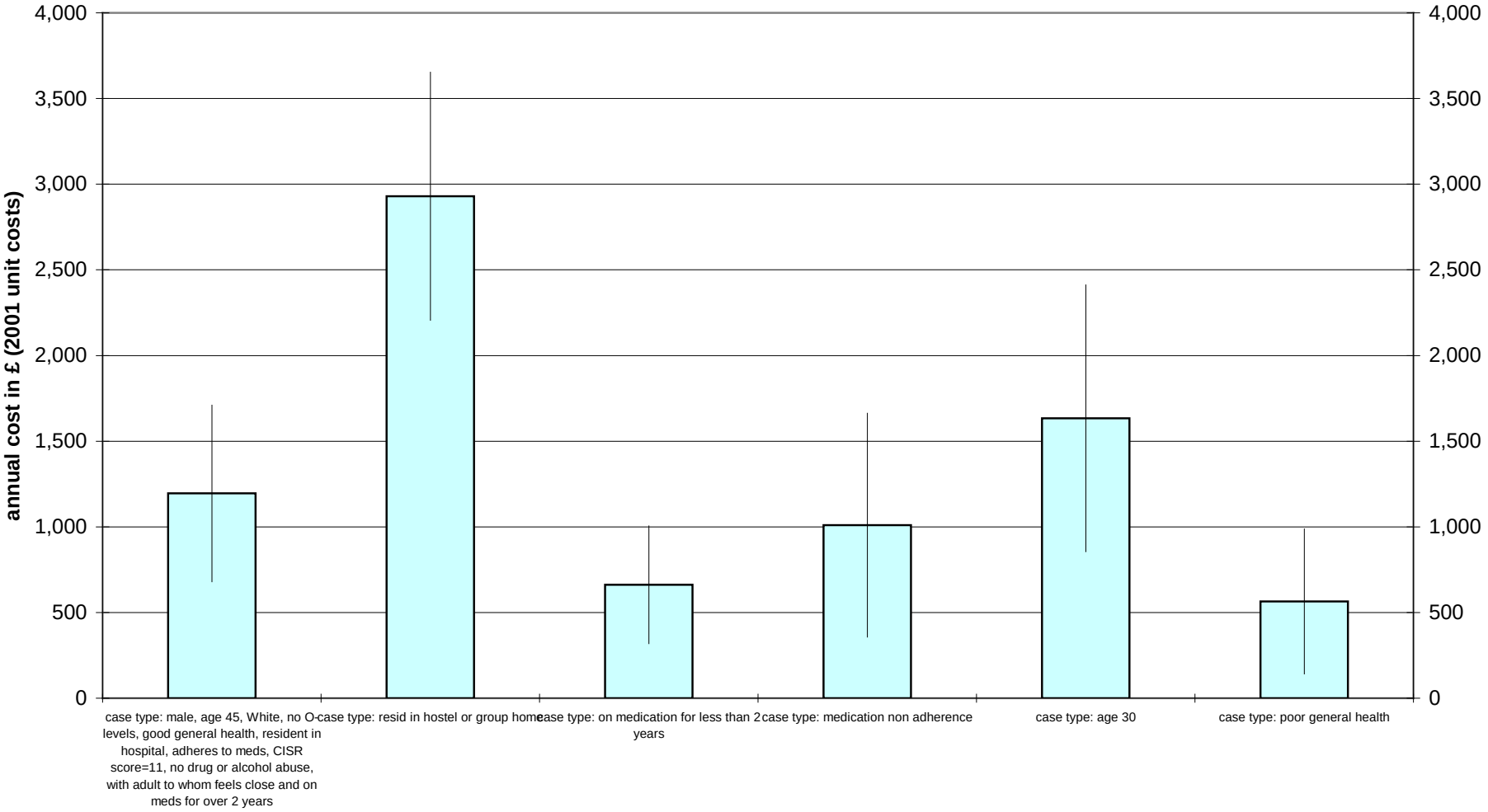


Table 3.11: Factors associated with total cost of services, PMS 1993-4 Institutions sample

Independent variables	N=657	
	Coefficient	95% CI
Resident in 'other' [1] institution (n=269)… …relative to resident in hospital (n=217)	-0.91***	-1.01, -0.82
Age	-0.0016	-0.0045, 0.0012
Male (n=335)… …relative to Female (n=151)	0.013	-0.064, 0.090
Higher qualifications or A-levels (n=55)…	0.059	-0.040, 0.16
O-levels (n=76)… …relative to below O-level qualifications (n=355)	0.016	-0.095, 0.13
Non-White (n=38)… …relative to White (n=448)	0.0026	-0.16, 0.16
Average general health (n=186)…	0.0078	-0.056, 0.072
Poor general health (n=66)… …relative to good general health (n=234)	0.035	-0.081, 0.15
CIS-R score [2]	0.00004	-0.0033, 0.0033
Non-adherent (n=91)… …relative to adherent (n=395)	0.089*	-0.010, 0.19
Lives with adult with whom feels close (n=298)... …relative to does not live with adult with whom feels close (n=188)	0.071*	-0.013, 0.15
Reports illegal drug use (n=46)… …relative to non drug users (n=440)	-0.069	-0.22, 0.078
Reports moderate or high alcohol dependence (n=31)... …relative to no alcohol dependence (n=455)	-0.035	-0.22, 0.15
Two or more years on medication(n=328)… …relative to less than 2 years on medication (n=158)	0.051	-0.032, 0.14
Constant	10.79***	10.61, 10.96
Link function	Log	
Distributional family	Gaussian	

* p≤0.10; ** p≤0.05; *** p≤0.01

[1] Residential care homes/group homes/hostels

[2] The Revised Clinical Interview Schedule (CIS-R) is used to assess minor psychiatric disorder. Higher scores indicate greater prevalence/severity of symptoms.

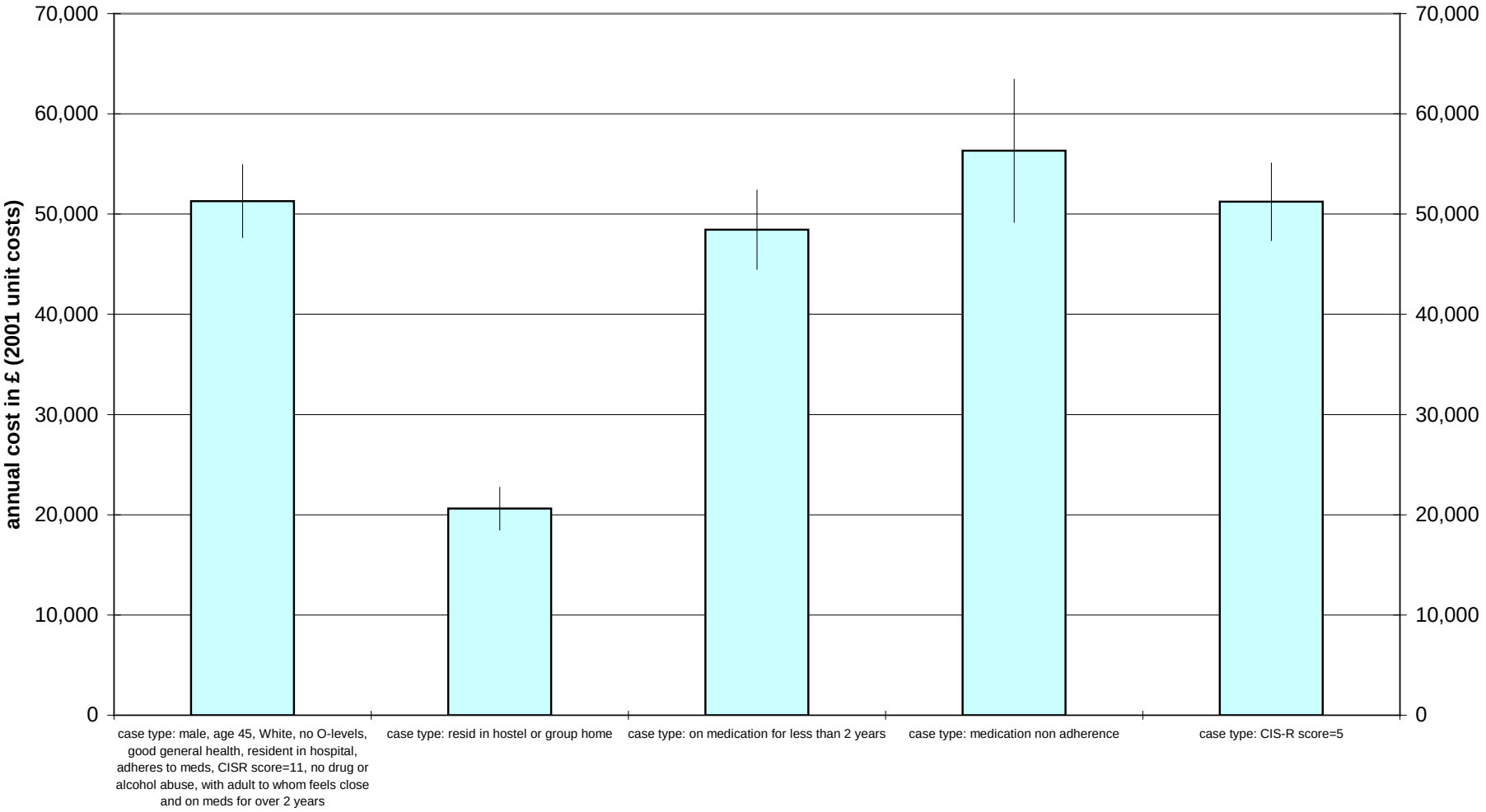
(p=0.079). Predicted total costs for residents of care homes, group homes and hostels were less than half of the amount for comparable hospital residents (see Figure 3.4). Predicted excess total service use costs for patients reporting non-adherence was over £5,000 per year.

3.3.5 Secondary analysis

Of the variables found to be associated with non-adherence in the institutions sample, age and having had a recent mental health inpatient stay were also found to be associated with non-adherence in the household sample (p=0.007 and p=0.020 respectively). As with patients in institutions, higher non-adherence was observed amongst younger respondents in the household sample. Likewise, having had a recent mental health inpatient stay was also univariately associated with non-adherence in the household sample. The homeless sample was half the size of the household sample and the univariate comparisons were only conducted where greater than 80% of the sample had non-missing data for the relevant variable. Of the variables associated with non-adherence within the institutions sample, this excluded analyses of the association of non-adherence and each of age and the CIS-R score. Both having had a recent mental health inpatient stay and experiencing side effects were associated with non-adherence in the homeless sample (p=0.037 in both cases).

The Wilcoxon rank-sum test comparing total service use costs across adherence status groups did not find a significant difference in the distribution of costs in the household sample (p=0.2070). Similarly, there was no difference in total costs between homeless respondents who reported adherence to their antipsychotic medication and those that reported non-adherence. However, both samples were extremely small (households: n=54; homeless: n=27) as it has been estimate that the number of persons with the illness in private households and homeless in England in the 2003/4 were 72,600; and 22,800 respectively (Mangalore and Knapp 2007).

Figure 3.4 **Predicted total health and social care costs, PMS 1993-4 Institutions sample**



3.4 Discussion

Analysis of the institutions sample of the PMS found significant associations between patient-related factors such as education and alcohol abuse. The experience of side effects was also significantly associated with non-adherence. With respect to service use and related costs, non-adherence was significantly associated with the use of external services, while the effect on non-adherence approached statistical significance in the use of inpatient services and the total cost of services.

3.4.1 Factors associated with non-adherence

Previous studies that have examined the factors that influence non-adherence in patients with schizophrenia or taking antipsychotic medication have typically been based on relatively small, local samples. Thus while there are inconsistencies between the findings of these studies, the differences may relate to the nature of the populations sampled or to reduced power due to small sample sizes. The Psychiatric Morbidity Survey has the advantage of being a large, nationally representative survey. I focused on people living in institutions (hospital and community-based) because analyses found high rates of missing data for the other data sets (that is, people living in households and people who were homeless).

The heterogeneity of results from previous studies may also be due to the setting in which the study took place. Results may differ due to changes in treatment regimes across time and location. At the time of the PMS survey interviews (1993-94), the majority of schizophrenia patients in the UK were prescribed older drugs. Atypical antipsychotics have been shown to be associated with different profiles of side effects (Geddes, Freemantle et al. 2000), and this may have influenced the association between side effects and non-adherence observed here. A trend towards lower non-adherence in patients receiving atypical medications has been observed elsewhere (Olfson, Mechanic et al. 2000; Sartorius, Fleischhacker et al. 2002).

A further difficulty in assessing the magnitude of the impact of non-adherence in the treatment of patients with schizophrenia is variability in the methods used to detect its presence. Some studies have employed patient-reported non-adherence, as in the PMS, while

others have used assessments by health care professionals. As discussed in chapter 2, the consistency in the assessment of non-adherence has not been established.

Factors that influence non-adherence are typically placed into one of three categories: patient-, medication- and environment-related (Oehl, Hummer et al. 2000). Among patient-related factors, the results are not consistent. Reviews by Fenton et al. (1997) and Lacro et al. (2002) showed inconsistency in the influence of age, gender and ethnicity, illness severity and the number of prior hospitalisations. However, they did observe greater consistency in the non-significance of education and income on non-adherence.

My results are at variance with this latter finding as I observed a significant association between education and non-adherence. Ruscher et al. (1997) found a similar association in a sample including a range of psychiatric patients and speculated that more educated patients may have a greater interest in, or feel more confident about, exercising control over their medication regimen. Better educated patients may also be more sensitive to and reflective about medication side effects.

As elsewhere (Trauer and Sacks 1998) I did not observe a relationship between gender and non-adherence. A review by Oehl et al. (2000) did report such a relationship and attributed it to poorer health care of men in general and the greater likelihood of women to be care-givers and thus with an incentive to take their medication. A trend exists in the sample for women to be in better health, though this result does not achieve statistical significance (chi-squared test p-value=0.108).

As noted earlier, the association between age and non-adherence is not universally observed, although my analysis does find such a link, with older people reporting better adherence (Coldham, Addington et al. 2002). My initial hypothesis was that this effect was related to patient insight and familiarity with medications over time. It has been shown that the longer the history of illness, the more likely patients are to adhere to their medications (Mojtabai, Lavelle et al. 2002). But testing the model without the effect of age did not make the index of medication familiarity significant in the model.

Illness severity was found to be associated with non-adherence. Patients with greater prevalence and severity of symptoms of neurosis and those who had an inpatient stay for a mental illness in the year prior to being interviewed were more likely to be non-adherent. The reviews by Fenton et al (1997), Kampman et al (1999)and Nose et al (2003) observed associations between non-adherence and the severity of psychotic symptoms.

Substance abuse is likely to increase non-adherence (Fenton, Blyler et al. 1997; Kampman and Lehtinen 1999; Olfson, Mechanic et al. 2000; Lacro, Dunn et al. 2002; Nose, Barbui C et al. 2003). A significant association was found in my analysis between alcohol abuse and non-adherence. Previous studies by Swartz et al. (2001) and Owen et al. (1996) have also observed this association, though Grunebaum et al. (2001) and Coldham et al. (2002) did not. However, the Grunebaum study was based on a relatively small sample, reducing the ability to observe significant effects, and focussed on patients in residential care settings where a low prevalence of substance abuse reflected the sobriety requirement that often exists in residential settings.

With respect to medication-related factors, I observed a significant association between past experience of side effects and non-adherence. It has been estimated that between 25% and 66% of patients on antipsychotics discontinue their medications because of side effects (Conley and Kelly 2001); akathisia being most highly associated with non-adherence (Fenton, Blyler et al. 1997) and weight gain also likely to be a key factor (Allison and Casey 2001). In a study examining the degree of moderate and severe distress of side effects the following ranking was reported: akinesia (40% of patients), weight gain (37.3%), anticholinergic (33.2%), sexual problems (30.8%) (Weiden and Miller 2001). The same study also found that side effects are under-reported by up to factor of four when relying on spontaneous report versus focused interview. Also, adherence has been found to be adversely affected by complex treatment regimens (Kampman and Lehtinen 1999).

Results of previous studies are inconsistent in the association found with the route of administration of medication (Fenton, Blyler et al. 1997), but adherence is more easily monitored in patients receiving depot injection, thus allowing for earlier intervention if non-adherence occurs (Oehl, Hummer et al. 2000)

3.4.2 The association between non-adherence and resource use and costs

Patterns of resource use and costs are associated with a range of patient characteristics, but differ by service type. Only non-adherence to medication appears to exhibit a consistent association with greater resource use, and is a significant factor in the use of inpatient and external services.

A significance association between non-adherence and service use and costs is observed by Glazer and Ereshefsky (1996) who concluded that measures taken to improve adherence are likely to decrease total direct treatment costs. Meta-analyses of data from a number of countries concluded that a 50% improvement in adherence would decrease one-year rehospitalisation rates by 12% (Weiden and Olfson 1995). Svarstad et al (2001) estimated the annual cost of hospital expenditures for schizophrenia patients on Medicaid in the US state of Wisconsin and found irregular medication users to cost, on average, an additional $1,620 per annum. This difference was statistically significant based on a linear regression analysis of log-transformed hospital costs that included age, sex, age of onset of illness, Global Assessment Scale score, alcohol or drug abuse, use of any oral neuroleptic and previous hospitalisations as covariates. The analysis of the PMS data found the effect of non-adherence to approach statistical significance in the use of inpatient services and when this result was combined with the effect on inpatient costs, the difference in costs for a hypothetical patient was over £2,500 per annum.

Eaddy et al (2005), using medical and pharmacy claims data from a large Southeastern Medicaid program in the US, found that inpatient hospitalisation charges were 54.5% greater for partially compliant patients as compared to compliant patients. This effect was statistically significant. Statistically significant differences were not found in this study when comparing total health care costs (including inpatient, outpatient and physician costs) for partially compliant patients with compliant patients. The effect of compliance was estimated using multivariate linear models of the log transformed charges with the total number of non-antipsychotic prescriptions, the total number of distinct non-antipsychotic medication classes, switching and augmentation and prior hospitalisation included as covariates.

Further evidence of a positive association between non-adherence and inpatient stays was observed by Weiden et al (2004) who used California Medicaid pharmacy refill and medical

claims data for 4,325 outpatients with schizophrenia. They found that the longer the gaps in use of medication (based on the medication possession ratio), the greater the odds of hospitalisation.

3.4.3 Other factors associated with resource use and costs

Symptom severity and patient satisfaction

The finding that costs of external service use were associated with severity of neurosis was consistent with results from a study comparing service utilisation in five European locations (Knapp, Chisholm et al. 2002). Further results from this study (EPSILON) indicate, however, that satisfaction with services was only weakly associated with demographic and clinical characteristics (Ruggeri, Lasalvia et al. 2003). It would be expected that satisfaction with services would be partly reflective of use of services.

Ethnicity

There exists limited published evidence on the relationship between ethnicity and service use in the treatment of schizophrenia. A US study found that among adolescents, Caucasian students received more services in the early stages of treatment than did African American students, but this difference diminished over time (Cuffe, Waller et al. 2001). A survey of US Medicare recipients found that among persons under age 65, Caucasians were one and a half times as likely as African Americans to receive an ambulatory care service and 1.3 times as likely to have received individual therapy. In a study based on data from the Fourth National Survey of Ethnic Minorities, among respondents with similar scores on the CIS-R, Caribbean respondents were less likely to have used therapist or social work services (Nazroo 1999).

My findings suggest that visible ethnic minorities are disproportionately more likely to access inpatient services and less likely to access external services. This suggests a substitution effect between these two types of services. It is possible that this pattern is the result of a differential response to symptoms by clinicians. For example, it may be the case that non-White patients are more likely than White patients to be admitted to inpatient care. Also, Nazroo (1997)

suggests that it is possible that if the instruments used underestimate rates of mental illness among certain ethnic minority groups, a larger proportion of those who were ill in these groups will not receive treatment. Another factor in this pattern of service use may be the effect of not having social support to encourage patients to access services. In the sample studied by Nazroo, 63% of White respondents reported that they lived with an adult with whom they feel close, while the corresponding rate for non-Whites was only 42%. A previous study suggested that the incidence of schizophrenia in non-White ethnic minorities increased significantly as the proportion of such minorities in the local population fell (Boydell, van Os et al. 2001), while another study showed that differences in the prevalence rate of psychosis between White British and African or African-Caribbean British samples were markedly reduced when social and economics factors were accounted for (Brugha, Jenkins et al. 2004). These results support the inference that social isolation is likely to influence the types of resources used for psychiatric services by individuals from ethnic minority backgrounds.

Residential care

A study of residents of psychiatric nursing homes found family contact to be associated with greater likelihood of service use (Anderson, Lyons et al. 2001). A secondary analysis of the PMS data that focussed on residents of residential care homes, group homes or hostels did not replicate this result. Those patients with one or more family members with whom they were close were no more likely to use inpatient services (odds ratio=0.83; 95% confidence interval = 0.32 - 1.34) or external services (odds ratio=1.43; 95% confidence interval = 0.60 - 2.25).

An interesting finding was that rates of external service use decreased as severity of neurosis increased. This result was consistent with a US-based study of residents of an intermediate care facility that also observed an inverse relationship between severity of illness and service use (Anderson and Lewis 1999). This result may occur because patients with more serious symptoms are more likely to be in a psychiatric hospital.

Age

Cuffel et al (1996) observed a non-linear relationship between age and service use. Total costs for schizophrenia were higher for the youngest (18-29) and the oldest cohorts (65-74 and 74+). My results did not indicate an association of this kind. In the analysis of the PMS institutions sample, only use of day activity services differed by age. As in the PMS, Svarstad et al (2001) did not observe age to have a significant effect on inpatients' hospital costs.

Drug use

Interestingly, patients who reported drug use incurred significantly lower costs when external services were accessed. This suggests that once accessed, relatively limited use of these services was made by these patients. This may reflect a lack of consistency on the part of drug users in accessing services.

Svarstad et al (2001) observed an association between alcohol or drug abuse and inpatient costs. This association was not found in analysis of the PMS data.

3.4.4 Limitations

A potential source of bias in the analysis of the PMS institutional sample arises from the poor rate of cooperation of institutions selected to take part in the survey. The rate of cooperation was poorest among private and smaller institutions. It may be the case, for example, that these cater to individuals with different levels of severity of illness as compared to larger institutions. As such, it is not necessarily the case that the results observed can be generalised to all individuals across the full range of accommodation types. Indeed, in the present context, it is the smaller institutions that are now more common in providing permanent residence to individuals with schizophrenia.

While the Psychiatric Morbidity Survey dataset offers advantages over some previously available data used to study non-adherence, there are measures not included that would have improved the analyses. As previously mentioned, establishing a strong therapeutic alliance between doctor and patient has previously been shown to be an important influence on

adherence (Olfson, Mechanic et al. 2000; Battaglia 2001; Grunebaum, Weiden et al. 2001), but is not measured in this dataset.

The analyses would also have been improved with inclusion of a measure of patients' attitudes towards their medication, their insight and cognitive functioning generally (Robertson, Woerner et al. 2002), and perceptions of their quality of life. A positive view of psychiatric medications and patient insight has been shown to improve adherence (Grunebaum, Weiden et al. 2001). These factors may be associated with the health belief model, which Oehl et al. (2000) suggests is a major determinant of adherence. The model establishes that adherence is related to a patient's perception of severity of illness, efficacy of treatment and ability to influence illness course. The debilitating nature of the illness, therefore, is thought to relate to lower health belief by the patient, and thus, poorer adherence.

The potentially important omitted variable bias created by some of the above factors not being available in the dataset was diminished by including the length of time on medication in the modelling, which is likely to be correlated with patients' attitutes towards medication and insight into their illness.

The models do not test for endogeneity due to the lack of suitable instruments in the dataset. It may be the case that service use may partly explain adherence, and therefore, in modelling the effect of non-adherence on service use I am missing the reverse causality that might be present. This simultaneity would lead to the estimate of the effect of non-adherence to be biased. Note, however, that if services do include reminders and encouragement regarding medication taking, the effect would be to improve adherence. Thus this effect would be counter to the effect that I am trying to observe – the effect of non-adherence. That is, the observed effect of non-adherence would be greater if simultaneity existed and was accounted for.

The cross-sectional nature of the Psychiatric Morbidity Survey data does not allow for analysis of the direction of causation in the associations between service use, costs and potentially associated factors. The analysis of the QUATRO study in the following chapter presents results where observations over time are collected. The PMS data also do not include information on the nature of the physician–patient relationship or attitudes towards service provision which may impact on individual decisions regarding use of services by patients

with schizophrenia. Also, supply-side factors could not be considered, although they are likely to impact on the availability of and access to services and hence on costs. In particular, inpatient services are sometimes used in place of less costly outpatient mental health services if the latter are not available (Sullivan, Jackson et al. 1996; Salvador, Haro et al. 1999).

The interpretation of significant vs. non-significant results is complicated by the potential co-linearity of variables. Preliminary analysis of the PMS data found significant associations between non-adherence and age, education, illness severity, alcohol abuse and residential setting. Other models with different combinations of variables were tested but here those that best summarised the associations found are reported.

Despite these limitations, the analyses are unusual in attempting to identify the factors associated with the use and cost of services by employing data from national, representative surveys. In particular, the link with non-adherence is examined closely. Robust statistical methods are used, increasing confidence in the associations reported. The 1993/4 PMS surveys were the only source of nationally representative data on psychiatric morbidity at the time this analysis was undertaken. I am aware that prescribing patterns have changed in the time since this data was collected. Most significantly, the newer class of antipsychotics, termed atypical antipsychotics, have become much more widely prescribed. I undertook research on the trends in antipsychotic prescribing and the factors associated with which type of antipsychotic was being prescribed in separate analyses which appear in appendix 2.

This analysis showed that the prescribing of the newer atypical antipsychotics in primary care practices increased significantly between 1993 and 1999, rising from 1.8% of antipsychotics prescribed in 1993 to 20.8% in 1999. It also found that older individuals were significantly less likely to be prescribed atypical antipsychotics. Individuals who had had a inpatient stay in the previous year were one-and-a-half times as likely to be prescribed the newer antipsychotics as compared to those who had not had a recent inpatient stay. Those individuals with more frequent primary care consultations were also significantly more likely to be prescribed the newer antipsychotics as compared to less frequent users of primary care. These results suggest that the newer antipsychotics were prescribed to patients found in my analysis to be significantly more likely to not adhere to their medication.

3.5 Summary

Patterns of resource use and costs are associated with a range of patient characteristics, but differ by service type. Only non-adherence to medication appears to exhibit a consistent association with greater resource use, and is a key factor in the use of inpatient and external services.

Important factors appear to relate to the degree of needs of the patient and the ability of the system to address them. For example, after standardising for severity of neurosis, drug misuse and other factors, the use of inpatient services and the costs incurred as a result of use are associated with being from a visible ethnic minority. Patients on medication for a significant length of time tend to make greater use of external services while being less likely to require inpatient services. The total cost of all services used was strongly associated with residence in hospital.

Chapter 4

The impact of non-adherence to medication in patients with Schizophrenia on health, social care and societal costs – analysis of the QUATRO study

4.1 Background and aims

Subsequent to completing the analyses of the PMS 1993/4 data reported in the previous chapter, another dataset was sought which would allow robust conclusions to be drawn regarding the associations between non-adherence and service use costs. As described in chapter 2 the features sought were that the data were nationally representative of the UK, sampled relatively recently, had an adequate measure of non-adherence, included comprehensive information on health and social care service use and indices of as many as possible of the potential covariates relevant to non-adherence and service use and collected these data at more than one time point to allow for analysis of changes over time. The Quality of Life following Adherence Therapy for People Disabled by Schizophrenia and their Carers (QUATRO) study was chosen for this analysis. While the study data was not nationally representative of the UK population, it met the other criteria.

The aim of analysis of the QUATRO study was to supplement the analyses of the previous chapter in determining the impact of non-adherence to medication on service use costs attributable to schizophrenia. QUATRO was a multi-national randomised controlled trial that evaluated an adherence therapy intervention for people with schizophrenia.

This analysis builds on the analyses of the Psychiatric Morbidity Surveys (PMS) described in the previous chapter in three important ways. Firstly the data are more up-to-date. Patients were recruited for the QUATRO study in 2002/3, whereas the Psychiatric Morbidity Survey interviews took place in 1993 and 1994 (Meltzer, Gill et al. 1996). A number of changes have taken place in the treatment of schizophrenia in the intervening period, most notably the introduction and sharply increased uptake of atypical antipsychotics (King and Knapp 2006). The newer medications have been argued to reduce side-effects (Sartorius, Fleischhacker et al. 2002; Sartorius, Fleischhacker et al. 2003), and therefore - other things being equal - are

likely to reduce rates of non-adherence. Also, as more patients now live in the community, rather than in hospital, they are less frequently in contact with care providers who, in residential or hospital settings, often provide reminders for medication taking.

Secondly, data are collected at two time points and therefore allow for longitudinal analysis. Longitudinal analysis is superior to cross-sectional modelling. If samples of the same size were used in each method, the longitudinal study provides greater statistical power. This is due to the fact that the intra-subject variability is significantly lower than the variability across subjects (Hedeker and Gibbons 2006). Also, because longitudinal studies allow one to follow the same individuals over time, they have the advantage of allowing for the analysis of dynamic responses. This, in turn, makes these studies better suited to make judgements as to the direction of causality in significant associations (Arellano 2003). Another advantage of longitudinal studies is that they allow ageing effects (i.e. changes over time within individuals) to be differentiated from cohort effects (i.e. differences between subjects at baseline), which cross-sectional studies do not allow (Hedeker and Gibbons 2006).

The third advantage of the QUATRO study relative to the PMS is that it included a wider range of service use contacts and considered non-health and social care costs which allowed me to take a wider perspective in assessing the impact of non-adherence to medication in schizophrenia on costs in society. With respect to costing services in schizophrenia, much of the costs to the patient, their family and the society as a whole are outside the health and social care system. For example, lost employment or employment in low-paid work are costs to both the individual and society that may result from a patient having schizophrenia. Criminal justice costs, the cost of informal care and the cost of lost employment are the non-health and social care related costs included in the costing of services reported in the QUATRO dataset. Mangalore and Knapp (2007) estimated that, in 2004/5, health and social care costs represented approximately 30% of total societal costs. They further estimated that annual cost of informal care, criminal justice costs and cost of lost employment for people with schizophrenia were £604 million, £1.1 million and £4.8 million respectively.

4.2. Methods

4.2.1 The QUATRO study

The QUATRO study was a multi-national randomized controlled trial carried out at four centres across four European countries (Germany, Italy, the Netherlands and the UK), funded by the European Union and coordinated from the UK. The sample was drawn from adults receiving care from psychiatric services in each of four European cities: Amsterdam (The Netherlands), Leipzig (Germany), London (United Kingdom) and Verona (Italy). Data collection took place between June 2002 and October 2003 (Gray, Leese et al. 2006). Each sample was recruited from the patient records of senior treating clinicians at a range of local in-patient and community settings that were typical of general treatment centres in the catchment areas of each site. The inclusion criteria were that the patient must have had a clinical diagnosis of schizophrenia, must require on-going antipsychotic medication for at least one year following the baseline assessment, and must have exhibited evidence of clinical instability in the year prior to baseline (Gray, Leese et al. 2006). Clinical instability is defined as meeting one or more of the following criteria: a hospital admission on mental health grounds, a change in the type or dose of antipsychotic medication, planned or actual increased frequency of contact with mental health services and indications of clinical instability reported by relatives, carers or the clinical team. Written, informed consent was obtained from all participants.

The study was a two-arm randomised controlled trial. Its main aim was to compare the effectiveness of adherence therapy with a health education control intervention (which allowed for therapist time and relationship) in improving health-related quality of life for people with schizophrenia receiving treatment from general adult mental health services in the four cities (Gray, Leese et al. 2006). Patients were randomly assigned to either receive the experimental intervention, an individual cognitive-behavioural approach which is collaborative and patient-centred, or a standard health education control intervention. The six elements that form the core of the cognitive-behavioural approach are assessment, medication problem-solving, a medication timeline, exploring ambivalence, discussing beliefs and concerns about medication, and using medication in the future.

Study participants were interviewed at baseline and after 12 months. Interviews were conducted by a researcher who was blinded as to the allocation of the participant to the intervention or control group, but the participants were not blinded as to which intervention they were receiving. Participants were not told, however, which of the two interventions was regarded by the study investigators as experimental.

Adherence to medication was based on patient responses on the Medication Adherence Questionaire (MAQ). Positive responses on the MAQ are summed to obtain a Morisky score (Morisky, Green et al. 1986). The Morisky score is a 5-point scale based on four questions relating to medication-taking behaviour. It asks patients if they ever forget to take medication, if they are careless about taking medication, if they ever stop taking medication once they feel better and if they ever stop taking medication because it made them feel worse. The Morisky score is widely used to assess adherence (Shalansky 2004; Day, Bentall et al. 2005). The total score on the scale ranges from 0 (all items rated 'yes') to 4 (all items rated 'no'). For the purpose of this analysis, values of 0 to 2 on the 5-point scale (0-4) were deemed as reflecting non-adherence as per the classification used by the QUATRO study team in their analyses (Gray, Leese et al. 2006). That is, individuals who responded in agreement with two or more of the medication-taking behaviour questions was classified as non-adherent.

The other main clinical measures assessed in the study were the mental component summary score on the Medical Outcome Study (MOS) 36-Item Short Form Health Survey (SF-36) and the Brief Psychiatric Rating Scale – Expanded (BPRS-E). The SF-36 is a self-report measure of health-related quality of life and well-being (Ware and Sherbourn 1992). The BPRS-E measures psychiatric symptoms, negative symptoms, depression and anxiety and manic excitement or disorganisation (Lukoff, Liberman et al. 1986; Ventura, Green et al. 1993).

The Client Service Receipt Inventory (CSRI) (Beecham and Knapp 1992) was used to collect service use data. The CSRI collects individual patient data on demographic characteristics, accommodation and living situation, employment history and earnings, including receipt of benefits, health and social care service receipt, and the role of informal carers. In the QUATRO study a three month retrospective period was used. Local language versions of the CSSRI-EU were available from the EPSILON study (Chisholm, Knapp et al. 2000), which

carried out a process of translation into local languages, focus groups and pilot activities to ensure face validity and semantic equivalence.

The study team had non-economist researchers administer the CSRI in face-to-face interviews with participants. Where there was a concern about the reliability of the reporting of service use, on account of a patient's mental illness, supplementary information from key workers, service providers and/or carers was sought to ensure that the information was as complete and reliable as possible.

The main finding of the QUATRO study investigators was that adherence to antipsychotic medication was not directly linked to quality of life in people with schizophrenia, but may be indirectly linked to quality of life through improvements in symptoms (Gray, Leese et al. 2006; Puschner, Born et al. 2006). The study investigators tested for differences in medication adherence attributable to the intervention but did not find significant differences (this analysis controlled for baseline MAQ score and site). A further analysis which restricted the analysis to a subgroup of the less treatment-adherent participants also found no significant difference between the groups at follow-up.

The primary outcomes of interest were the direct health and social care costs and societal costs. Health and social care costs included the cost of medication(s), special (non-hospital) accommodation, inpatient stays (including the cost of accommodation), outpatient visits, community-based day services and community-based professional contacts. The individual items from the questionnaire included in each of these health and social care cost categories, as well as those that were included as criminal justice and informal care costs, appear in Table 4.1.

Societal costs included health and social care costs, criminal justice, and informal costs as well as the cost of lost employment. All unit costs were estimated at 2003 price levels. This year was chosen as it corresponds to the period of time when the trial took place. Unit costs were estimated in each study site using either suitable national costs or local service activity and finance data (Patel 2006). Based on the human capital approach, the national average wage was used to estimate the cost of time off work. The national average wage was also used to estimate the cost of informal care based on the opportunity cost method. Because the study

Table 4.1: Health and social care services and benefits included in analyses, QUATRO study

Health and social care services	Medication	
	Special accommodation	
	Hospital inpatient stays	
	Hospital outpatient visits	Psychiatric outpatient department Day hospital visits
	Community-based day services	Community mental health centre Day activity centre Group therapy Sheltered workshop Specialist education
	Community-based professional contacts	Community Psychiatrist Community Psychologist GP District Nurse Community Psychiatric Nurse Social worker Occupational therapist Home help/home care worker
Criminal Justice		Police contacts Nights in police cell or prison Psychiatric assessments Criminal court appearances Civic court appearances
Informal care		Childcare Personal care Help in/around home Help outside home Other care

centres were across four countries, it was necessary to convert unit costs to a common currency. The costs were adjusted to purchasing power parity (PPP)-adjusted Euros (Patel 2006).

4.2.2 Statistical methods

To assess the effect of an intervention in a trial with measurements taken of the outcome of interest before and after the intervention, the most appropriate method is the difference-in-difference model (Meyer 1995). The standard difference-in-difference equation is:

$$y_i = \beta_0 + \beta_1 * treat_i + \beta_2 * time_i + \beta_3 * (treat_i * time_i) + e_i$$

where $treatment_i = 1$ if in the treatment group or $treatment_i = 0$ if in the control group and $time_i = 0$ if outcome was assessed at baseline or $time_i = 1$ if outcome was assessed at followup. This model accounts for changes that may be occurring over time that are not due to the treatment. An example often given for the application of the difference-in-difference model is that of the effect of a new policy within a particular region. A model that attempted to determine the impact of the policy change by simply comparing values on the outcome of interest before and after the intervention assumes that there are no other changes taking place at the same time as the intervention that may be impacting the outcome. The difference-in-difference model identifies a control group similar to the group receiving the intervention. In the example, say another region that did not introduce the policy change. The diffence-in-difference model estimates the change over time in this control group and compares it to the change over time in the group that received the intervention. In doing so, this model can more accurately identify the effect of the intervention as the difference on the outcome that occurred within the treatment group over and above the difference in the outcome that occurred in the control group. In the notation above, the coefficient of the interaction term, β_3, is the difference-in-difference estimate of the treatment effect. That is, this is the effect of treatment after the intervention over and above the effect of any treatment effect at baseline.

In the case of the model I wanted to estimate, I was primarily interested in the effect of adherence before and after treatment where individuals were randomised to receive treatment

or control. An indicator of adherence status was added to the model, as was its interaction with treatment. I have assumed that there was no interaction between time and adherence. That is, there was no reason to think that the effect of adherence status on the outcome of interest, costs, will be different at baseline as compared to at follow-up. I also added to the model covariates that were deemed relevant to the analysis of associations with health, social care and societal costs. The model becomes:

$$y_i = \beta_0 + \beta_1 treat_i + \beta_2 time_i + \beta_3 (treat_i * time_i) + \beta_4 nonadh_i + \beta_5 (treat_i * nonadh_i) + \beta_6 \overline{X_i} + e_i$$

where $nonadh_i = 1$ if the patient is judged to be non-adherent or $nonadh_i = 0$ if the patient is judged to be adherent. A significant interaction between adherence status and treatment would imply that the effect of adherence on costs would be different according to whether or not the individual had received treatment or not. I would not expect this to be the case. This is different from saying that there is an association between receipt of treatment and adherence status which suggests that receipt of treatment affects adherence.

The model I wanted to fit differs, however, from the standard difference-in-difference model in that individuals are randomised to the treatment and control group and as such, differences between the two groups at baseline are due to chance alone. As it can be assumed that there is no difference between the groups before the intervention, I assigned a value of 0 to treatment for all individuals at baseline to reflect the fact that at this point no actual treatment was received. That is, for those patients who were randomised to treatment, a value of 0 would be assigned at baseline as they had not yet received any treatment. Since it can be assumed that randomisation eliminated any differences between the two groups, measuring the effect of randomisation on costs would be redundant. Assigning a value to treatment which reflects the actual state of the individual with regards to receipt of treatment at each time point is the appropriate model structure for the design of this study and the model I wanted to fit.

In this case the model reduces to:

$$y_i = \beta_0 + \beta_1 treat_i + \beta_2 time_i + \beta_3 nonadh_i + \beta_4 (treat_i * nonadh_i) + \beta_5 \overline{X_i} + e_i$$

as the treatment variable and treatment by time interaction take on identical values for every observation. If the interaction between adherence and treatment is significant, the effect of non-adherence on costs is β_4 for those who did not receive treatment and the linear combination of $\beta_4+\beta_5$ for those who did receive treatment.

The notation $\overline{X}$ represents a vector of patient-specific covariates. The model sought to control for the following variables identified in the dataset as potentially relevant to the cost outcomes: age, sex, whether or not the patient lived alone, their study site, education level, ethnicity and familiarity with medication. The significance of the treatment, time and study site variables are not commented on here as these were not the focus of my analyses. The results reported focus on non-adherence and individual patient characteristics. The effect of time on costs are not commented on although it is assumed that cost will reduce over time. The effect of study site on costs are interesting, but may in part be due to how services are organised within each site which is not the focus of this study.

Age was included in the modelling as a continuous variable. Age was assessed at the time of the initial interview. Education was measured as a dichotomous variable distinguishing those who had completed further or tertiary education from those who had not. Ethnicity was also a dichotomous variable distinguishing White Europeans from all other ethnic backgrounds. It is likely that the effect of ethnicity may not be consistent across minority ethnic groups, but the limited sample size made it infeasible to test for differences between specific minority ethnic groups. The length of time on medication was used as an index of familiarity with medication and was modelled as a continuous variable.

In cases where missing values result in only one of a pair of observations from a particular respondent entering in the model, the one observation was retained as it still provides information as to the relationship between the outcome and explanatory variables.

The cost of treatment itself was not included in the measure of costs used as the outcome as this would be in effect replicating a difference in the treatment and control groups that is accounted for by having a treatment effect in the model. Therefore, in relation to the treatment effect, I wanted to know differences in cost over and above the cost of treatment.

Analysis of the PMS 1993/4 Surveys in chapter 3 had suggested that looking at the component services seperately may reveal some associations between non-adherence and the costs associated with specific services, even where there was not a significant association between non-adherence and total health and social care costs. Additional models were estimated using the QUATRO dataset to look at those component costs that were used by a large proportion of the sample and significantly contributed to total costs. The component costs analysed were inpatient, community-based day service and informal care costs.

Due to the skewness in the distribution of the cost data, GLM models were estimated with the Park test employed to determine the appropriate distribution and link functions. It was expected that the Park test would suggest a Gamma function as this is the natural distributional family for skewed continuous values as were the measures of costs attributable to illness. A Poisson distribution is usually used for skewed count values (e.g. number of visits to GP).

Robust standard errors were estimated. The robust option accounts for heterskadisticity – a non-random pattern in the error terms. This is separate from correcting for the within-individual correlation in the error term. In the GLM procedure in STATA, the 'cluster' command will account for this correlation.

In the analyses of some of the component costs, it was necessary to undertake two-part modelling. This was because a number of patients did not use a particular subset of services. In this case, they would have cost values of zero. If a substantial number of individuals have zero values a two-part model is recommended (Mullahy 1998). Firstly, a logistic regression model was run on the outcome of whether or not costs were incurred. The second part of this approach was then to run a GLM on the costs for the subsample of patients who did use the service being modelled. That is, the patients who did not use the service are excluded from the second stage GLM modelling.

Analysis was undertaken using the STATA 10.1 software package (STATA 10.1 2009). Significance values below 0.05 were deemed statistically significant.

4.3. Results

4.3.1 Demographics

Four hundred and nine adults were recruited from across the four sites. The mean age of the sample was 42 years and 60% of the sample were male (see Table 4.2). Over 30% of the sample had educational qualifications above the secondary school level, and on average, the sample had been prescribed antipsychotic medication for over 13 years, reflecting the chronic nature of their illness. Approximately 30% of respondents had Morisky scale scores reflecting non-adherence to their medication.

Of the initial 409 patients interviewed at baseline, 357 completed both interviews. There were no significant differences on the demographinc indices between the individuals who did not complete a follow-up interview and those who did (see Table 4.2).

Table 4.3 presents the demographic variables by study site. The mean age and years on antipsychotic medication were similar across sites. The sample from Amsterdam included a greater proportion of men as compared to the other sites. The Amsterdam and London samples were ethnically diverse while the Leipzig and Verona samples were not. A greater porportion of London sample members reported completion of tertiary or further education. Verona sample members were also less likely to live alone relative to the other sites. The rate of non-adherence at baseline was low and differed widely across the four sites. In Leipzig, London and Verona the percentage of the sample with Morisky scores of 0 to 2, and therefore indicating non-adherence, were 32.3%, 48.9% and 30.8% respectively. In Amsterdam, however, 11.2% of the sample registered Morisky scores at that level. This value seems unusually low given that estimates are that between 20% and 80% of schizophrenia patients do not adhere to their medication (Battaglia 2001; Conley and Kelly 2001). The scores on the BPRS-E were significantly lower within the Dutch sample, which suggested less severe symptoms within this subsample.

Table 4.2: Characteristics of QUATRO study sample at baseline**:** overall, completers and non-completers

Characteristic	*Completers (n=357)*	*Non-completers (n=52)*	*Overall (n=409)*
Centre: N (%)			
Amsterdam	87 (24.4)	13 (25.0)	100 (24.5)
Leipzig	81 (22.7)	16 (30.8)	97 (23.7)
London	80 (22.4)	12 (23.1)	92 (22.5)
Verona	109 (30.5)	11 (21.2)	120 (29.3)
Age: mean (sd)	41.7 (11.5)	40.3 (11.4)	41.5 (11.5)
Sex: % male	59.9%	59.6%	59.9%
Ethnicity: % White European	75.1%	80.8%	75.8%
Education: % with further/tertiary qualifications	32.4%	32.7%	32.4%
Years using antipsychotics: mean (sd)	13.9 (9.9)	11.6 (9.8)	13.7 (9.9)
Living situation: % living alone	40.2%	42.3%	40.4%
Morisky scale total score: mean(sd)	3.0 (1.2)	2.9 (1.2)	2.9 (1.2)
Percent non-adherent to medication at baseline *	30.5%	28.2%	30.3%
SF-36 mental component score: mean (sd)	39.1 (11.9)	40.1 (10.7)	39.2 (11.7)
BPRS-E total score: mean (sd)	45.0 (13.0)	46.1 (13.5)	45.2 (13.0)

* based on Morisky total scores of 0, 1 or 2 indicating non-adherence

Table 4.3: Characteristics of QUATRO study sample at baseline**:** overall and by study site

Characteristic	*Amsterdam (n=100)*	*Leipzig (n=97)*	*London (n=92)*	*Verona (n=120)*	*Overall (n=409)*
Age: mean (sd)	40.0 (10.2)	38.7 (10.7)	42.5 (11.7)	44.3 (12.4)	41.5 (11.5)
Sex: % male	73.0%	56.7%	54.4%	55.8%	59.9%
Ethnicity: % White European	44.0%	100%	53.3%	100%	75.8%
Education: % with further/tertiary qualifications	19.0%	27.8%	54.4%	30.5%	32.4%
Years using antipsychotics: mean (sd)	12.7 (9.2)	11.6 (8.7)	15.8 (11.4)	14.3 (9.7)	13.7 (9.9)
Living situation: % living alone	43.0%	55.2%	40.2%	26.7%	40.4%
Morisky scale total score: mean (sd)	3.6 (0.9)	2.8 (1.3)	2.5 (1.2)	3.0 (1.2)	3.0 (1.2)
Percent non-adherent to medication at baseline *	11.2%	32.3	48.9	30.8	30.3%
SF-36 mental component score: mean (sd)	41.7 (11.5)	34.7 (11.3)	40.2 (12.0)	40.2 (11.1)	39.3 (11.7)
BPRS-E total score: mean (sd)	37.5 (10.2)	48.3 (15.7)	46.1 (11.1)	48.3 (11.5)	45.2 (13.0)

* based Morisky total scores of 0, 1 or 2 indicating non-adherence

Four patients were missing data on two of the factors identified as potentially being associated with costs. A further 51 were missing data on one variable only. Length of time on medication was the variable with the most missing data. These data were not provided by 43 individuals. Other variables with missing data were the Morisky self-assessed adherence score which was missing for 13 patients, level of education which was not reported by two patients and whether or not they lived alone which was missing for one patient.

Excluding the variable on length of time on medication would thus reduce the number of observations in the dataset by 10%. In deciding whether or not to use multiple imputation, the key criteria is whether or not the missing values can be assumed to be missing at random. That is, the data being missing was not conditional on their values or the value of the dependent variable. In the case of length of time on medication, it not obvious as to why a patient would be more or less likely to report this information based on the length of time they were on medication. Similarly, there would be no reason to not report this information based on their service use. Thus this variable was assumed to be missing at random and multiple imputation was performed to replace the missing data. There are potential reasons, however, why a patient would not want to disclose that they had a low level of educational qualifications, lived alone or had not taken their medication. For this reason, and the fact that relatively very few observations would be lost by excluding observations where one of these three variables were missing, missing values on these variables were not imputed.

4.3.2 Distribution of costs

Table 4.4 presents the distribution of baseline costs across all patients in the sample. Among those who used health and social care services, the mean cost was approximately €26,000 and the median €11,200. The mean value being greater than the median value reflected the fact that these costs were significantly skewed to the right. The mean societal cost was approximately €33,000 and these costs were similarly skewed. The median societal cost incurred was €19,500. The two services most influencial on health and social care costs at baseline were inpatient visits and non-hospital accomodation costs (median costs of €10,720 and €29,230 respectively). The latter costs were incurred, however, by fewer than 35% of the sample. Inpatient costs were reported by approximately half of the sample.

Table 4.4: Distribution of costs at baseline, QUATRO study (in PPP Euros)

	Number of users	Mean	Standard Deviation	Median	Interquartile range	Min	Max
Medication	388	€4,022	€5,869	€2,348	€550-€4,400	€3	€41,371
Inpatient	189	25,767	34,145	10,720	4,998-30,346	398	172,628
Outpatient	140	1,366	3,369	557	551-1,101	55	36,236
Community-based day services	147	9,484	32,910	1,001	331-4,935	13	243,426
Community-based professional contacts	371	1,065	2,085	604	292-1,107	13	34,149
Accommodation – non-hospital	70	33,009	15,041	29,227	25,894-40,065	4,484	56,966
Total health and social care	**401**	**25,959**	**35,134**	**11,202**	**3,750-38,013**	**211**	**270,495**
Informal care	201	10,163	16,087	3,599	1,611-10,798	474	112,713
Criminal justice	31	4,859	14,282	336	336-1,527	82	59,001
Absenteeism	37	15,143	16,804	5,449	2,071-27,531	463	50,134
Societal costs	**398**	**32,946**	**38,161**	**19,506**	**5,912-48,244**	**211**	**276,178**

The costs associated with days off work were substantially higher than those of informal care, but few respondents reported incurring these costs. This was, in part, a result of less than 20% of the sample reporting being in paid employment at baseline.

Table 4.5 lists the estimates of health and social care costs and societal costs, at baseline, across the four study sites. The vast majority of patients in each site incurred health and social care costs. These costs varied significantly across sites, with the median ranging from approximately €44,050 in Leipzig to approximately €8,270 in London. The median societal costs, at baseline, were highest in Amsterdam, followed by Leipzig, London and Verona.

The median component costs are compared across the study sites in Table 4.6. Data on the percentage of individuals in each sample site who used each of the services is also included in the table. Some interesting patterns emerge from these data. For example, within the Dutch sample, where inpatient and community-based day services were used, the costs incurred are higher than in the other sites. Inpatient services were more frequently used in Leipzig as compared to the other sites, with non-hospital accomodation less frequently used in this site. Outpatient services were more commonly used and the cost of community-based professional contacts were higher in London as compared to the other sites. Also, informal care was more widely reported, and at a higher cost, in London.

4.3.3 Health and Social Care costs

The first model estimated the significance of non-adherence and other factors on health and social care costs. In this model, 770 observations, across the two time points, contributed to the analyses. A single GLM model was estimated as all individuals with complete data across the independent variables incurred health and social care costs. The model determined that the effect of non-adherence was not statistically significantly associated with health care costs (see Table 4.7). Of the remaining factors considered, significantly higher costs were incurred amongst those that lived with others as compared to those who lived alone and females incurred significantly lower health and social care costs than did men. None of the other individual characteristics were significantly associated with these costs.

Table 4.5: Distribution of baseline (i) health and social care and (ii) societal costs in QUATRO study sites (in PPP Euros)

	Health and social care costs				Societal costs			
	Number of users	Mean	Median	Interquartile range	Number of users	Mean	Median	Interquartile range
Amsterdam (n=100)	97	42,802	36,315	5,480-71,188	96	46,207	37,676	6,640-72,710
Leipzig (n=97)	95	28,382	44,067	7,651-31,722	95	37,035	26,514	12,515-44,351
London (n=92)	90	16,195	17,623	3,755-30,258	90	25,631	18,372	8,474-34,246
Verona (n=120)	119	17,679	4,994	1,923-20,360	117	4,374	9,669	3,848-39,954

Table 4.6: Distribution of health and social care and societal cost components at baseline in QUATRO study sites (in PPP Euros): Median cost (% of sample that used service)

	Amsterdam (n=100)	Leipzig (n=97)	London (n=92)	Verona (n=120)
Medication	€2,227 (92)	€4,058 (99)	€1,736 (96)	€1,774 (100)
Inpatient	54,784 (45)	10,142 (78)	7,875 (37)	5,579 (28)
Outpatient	397 (25)	1,236 (13)	551 (76)	675 (27)
Community-based day services	4,524 (32)	719 (30)	1,001 (42)	902 (39)
Community-based professional contacts	430 (84)	446 (84)	946 (98)	487 (97)
Accommodation – non-hospital	36,989 (29)	19,297 (4)	29,227 (22)	40,065 (14)
Total health and social care	36,315 (97)	17,623 (98)	8,271 (98)	4,994 (99)
Informal care	1,611 (41)	5,209 (51)	6,779 (63)	3,599 (44)
Criminal justice	1,007 (7)	336 (18)	336 (4)	336 (3)
Absenteeism	20,389 (10)	16,348 (7)	2,294 (5)	3,625 (13)
Societal costs	37,676 (96)	26,514 (98)	18,372 (98)	9,669 (98)

Table 4.7: Generalised linear model of factors associated with health and social care costs – QUATRO study

Potentially associated factors	*N=770*	
	Coefficient	*95% Confidence Interval*
Treatment… …relative to no treatment	-0.091	-0.40, 0.22
Time 1(follow-up)… …relative to Time 0 (baseline)	-0.29***	-0.49, -0.08
Non-adherent… …relative to adherent	-0.12	-0.37, 0.14
Intervention x Non-adherence interaction	0.51	-0.14, 1.16
Age – 5 year increment	0.017	-0.044, 0.079
Females… …relative to males	-0.27**	-0.52, -0.023
Lives alone… …relative to lives with others	-0.40***	-0.65, -0.15
Amsterdam (The Netherlands)… Leipzig (Germany)… Verona (Italy)... ...relative to London (UK)	0.80*** 0.45** -0.10	0.50, 1.10 0.045, 0.86 -0.46, 0.26
Education – further or tertiary... ...relative to primary, secondary or general	0.084	-0.16, 0.33
Not White European… …relative to White-European	-0.23	-0.51, 0.046
Number of years on medication	0.0027	-0.011, 0.016
Constant	9.91***	9.36, 10.46
Link function	Log	
Distributional family	Gamma	

* p<0.10; ** p<0.05; *** p<0.01

Figure 4.1 illustrates the relative impact on health and social care costs of non-adherence and the factors found to be significantly associated with these costs. A hypothetical reference case of a woman, aged 45, of White European ethnicity, without tertiary or further (post-secondary) education, resident in London, who adhered to medication, lived with others, received adherence education and had been on medication for one year was estimated by the model to have incured health and social costs of approximately €17,700 in the three months prior to the follow-up visit. Altering the combination of factors such that this case was that of a man (all other characteristics remaining the same), the model estimates additional costs of over €5,400. Living alone was associated with a €5,800 reduction in costs relative to the base case. Altering the ethnicity to that of somone not White European was associated in the model with a €3,800 reduction in costs relative to the base case. A €5,000 reduction in costs was associated with altering the base case to that of someone who does not adhere to their medication. Note, however, that across the full range of potential values for the remaining variables considered in the model, the effect of non-adherence was not found to be statistically significant.

4.3.4 Societal costs

Societal costs were estimated as the sum of health and social care, informal care, criminal justice and absenteeism costs. As with health and social care costs, a two-part model was unnecessary as these costs were incurred for all individuals with complete data on the independent variables. In the model assessing factors for their association with societal costs, those who reported non-adherence did not differ from those reporting adherence (see Table 4.8; p=0.186). The interaction between treatment and non-adherence approaches statistical significance (p=0.090) suggesting that the effect of non-adherence on societal costs is different for those who received treatment compared to those who did not. A test of the linear combination determined that the effect of non-adherence for the latter group was also not significantly different from zero (p=0.212).

Figure 4.1

Predicted health and social care costs, QUATRO study

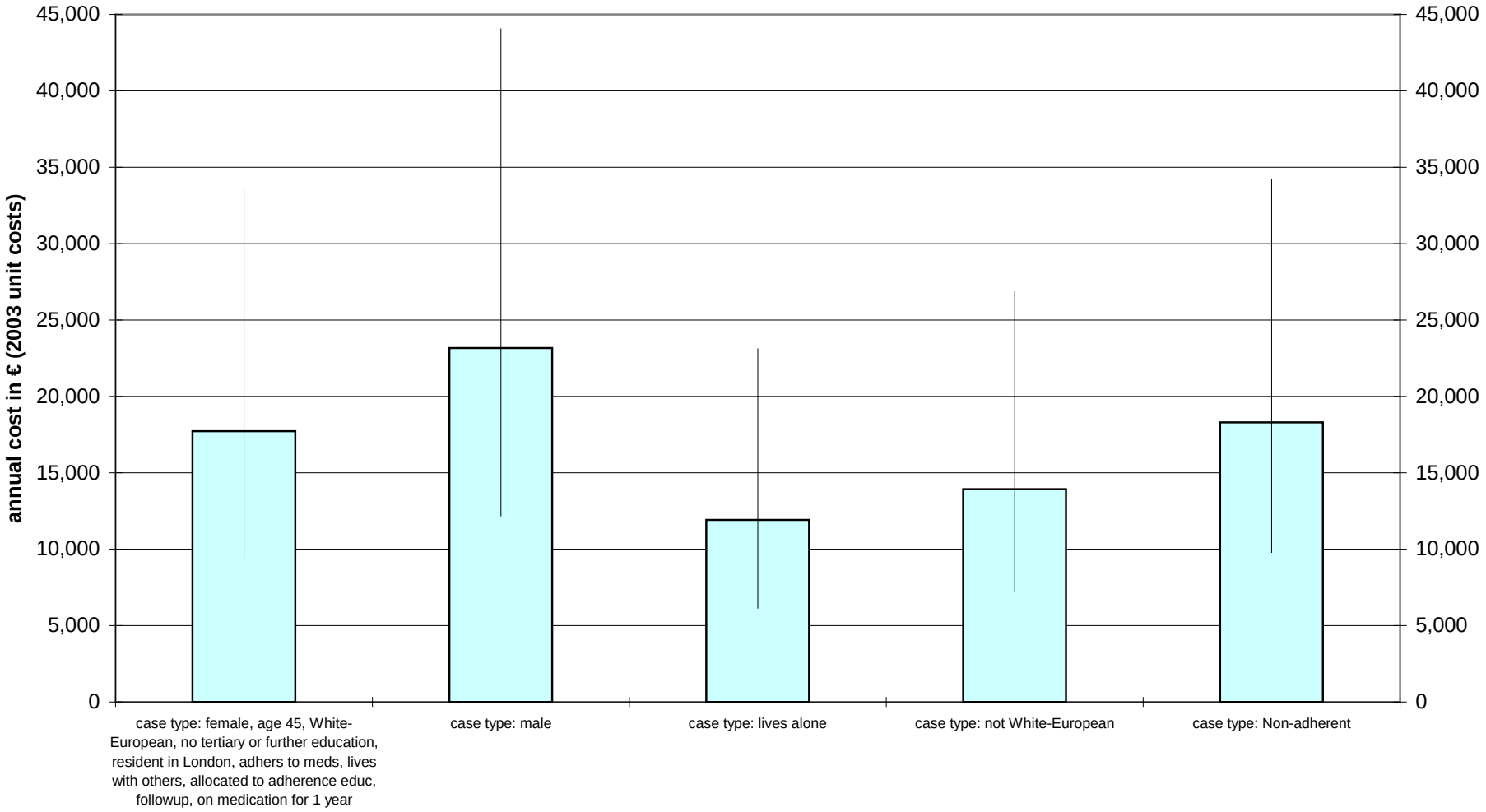


Table 4.8: Generalised linear model of factors associated with societal costs, QUATRO study

Potentially associated factors	*N=770*	
	Coefficient	*95% Confidence Interval*
Treatment… …relative to no treatment	-0.065	-0.35, 0.22
Time 1(follow-up)… …relative to Time 0 (baseline)	-0.33***	-0.51, -0.16
Non-adherent… …relative to adherent	-0.16	-0.38, 0.063
Intervention x Non-adherence interaction	0.48*	-0.076, 1.04
Age – in 5 year increments	-0.025	-0.080, 0.030
Females… …relative to males	-0.037	-0.25, 0.18
Lives alone… …relative to lives with others	-0.39***	-0.61, -0.16
Amsterdam (The Netherlands)… Leipzig (Germany)… Verona (Italy)... ...relative to London (UK)	0.49*** 0.15 -0.22	0.22, 0.76 -0.19, 0.50 -0.53, 0.087
Education – further or tertiary... ...relative to primary, secondary or general	0.17	-0.040, 0.38
Not White European… …relative to White European	-0.40***	-0.64, -0.15
Number of years on medication	0.0036	-0.0085, 0.016
Constant	10.60***	10.13, 11.07
Link function	Log	
Distributional family	Gamma	

* p<0.10; ** p<0.05; *** p<0.01

As with the model of health and social care costs, those who lived with others had significantly higher societal costs as compared to those who lived alone. Additionally, White Europeans had significantly higher costs as compared to repondents of other ethnicities.

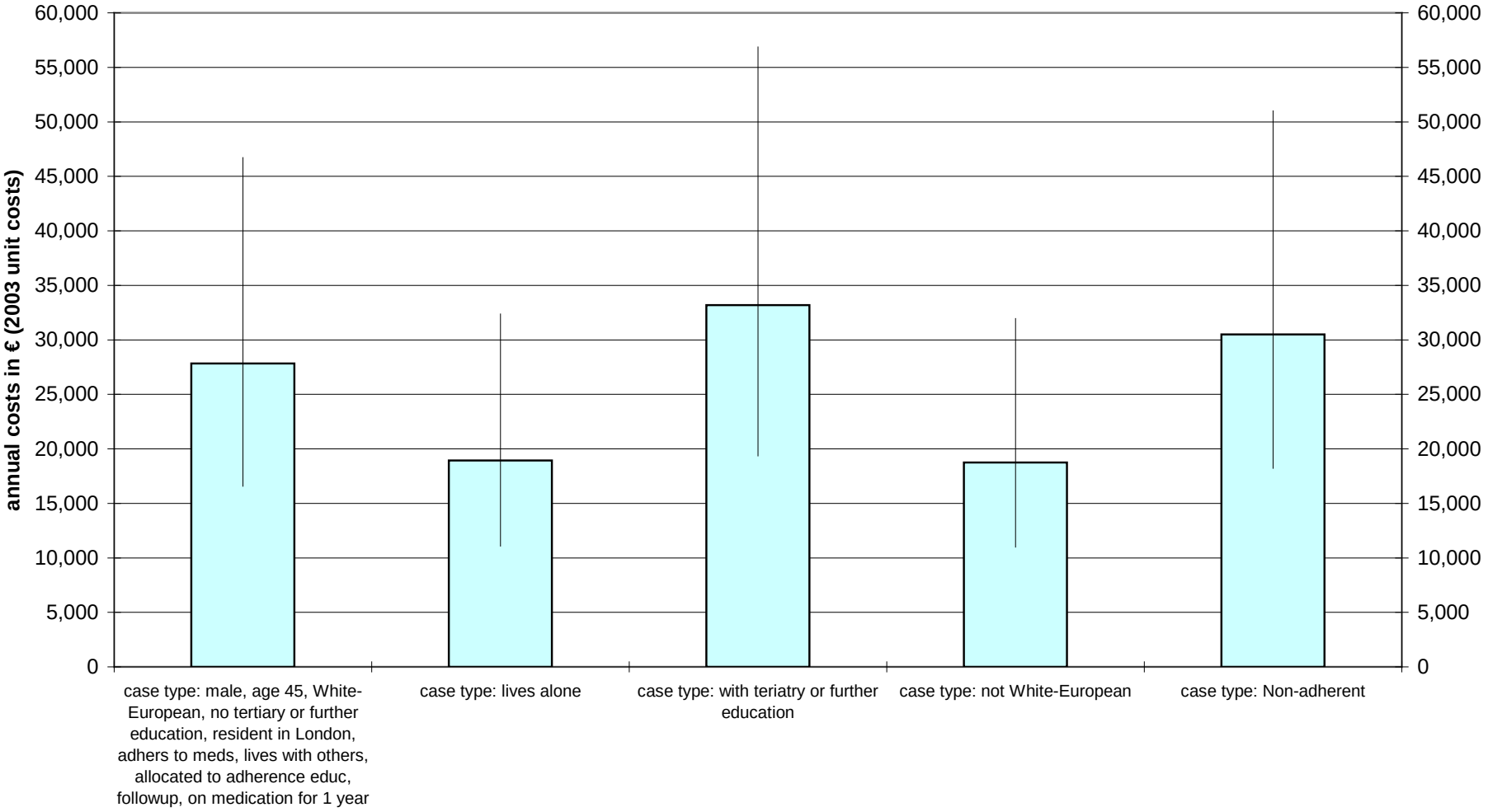
The relative magnitude of these effects on predicted societal costs are illustrated in Figure 4.2. The base case was chosen as a man, aged 45, of White European ethnicity, without tertiary of further education, resident in London, who adhers to his medication, lives with others, received adherence education and was on medication for 1 year. The model predicted that for this hypothetical case, societal costs at follow-up would be €27,830. The effect of changing the base case to that of someone living alone reduced the predicted societal costs by €8,900 as compared to the base case. A similar reduction in costs would be expected if the case was changed to that it was of a non-White European. A change to the educational level of the base case to having tertiary or further education increases the predicted societal costs by €5,350 relative to the base case. An individual with the same characteristics as in the base case but who was non-adherent was predicted by the model to incur €6,380 less in societal costs at follow-up.

4.3.5 Component costs

Analyses were undertaken to determine if any of the individual services that were key components of overall costs were associated with non-adherence. These analyses may help determine which, if any, particular types of services used by people with schizophrenia were strongly impacted by non-adherence. The services deemed to be most influencial on total costs, both in terms of the number of users of the service and the costs incurred, were inpatient visits, community-based day services and informal care. Within each of these, a significant number of individuals in the sample did not use the service and therefore, two-part models were used. Recall that the first part of the two-part model uses a logistic regression model to assess factors for their association with whether or not the service was used and the second part uses a GLM to assess factors for their association with the costs incurred within the subsample of individuals who used the service.

Figure 4.2

Predicted societal costs, QUATRO study



Inpatient stays

The logistic regression model found that individuals who lived alone were less likely to have had an inpatient stay as compared to those who lived with others. None of the other individual characteristics considered was significantly associated with having had an inpatient stay (see Table 4.9). The model correctly predicted whether or not inpatient stays had occurred for 65% of cases. The link test p-value for this model was 0.2976 suggesting that the model was not misspecified, and the likelihood ratio, Pearson's and Hosmer-Lemeshow test p-values suggested acceptable goodness of fit.

With respect to inpatient costs, the GLM model found that inpatient costs were not significantly associated with any of the factors considered. The interaction of treatment and non-adherence approached statistical significance (p=0.077), suggesting that the effect of non-adherence on inpatient costs was different for those who received treatment compared to those who did not. There was a trend towards inpatient costs being significantly higher for this group (p=0.083). Thus for those not receiving the study intervention (or prior to receiving the intervention), the effect of non-adherence was not significant. Receipt of treatment was associated with a trend towards non-adherence being associated with higher costs.

There was also a trend for ethnic minority respondents to have lower inpatient costs as compared to White European respondents (see Table 4.10; p=0.060). Because the factors considered did not appear to be associated with inpatient costs, predictions for case types comparing costs were not estimated.

Community-based day services

The next key group of services modelled were community-based day services. In a logistic regression model of whether or not these services were used, living alone and time on medication were significant (see Table 4.11). Individuals who lived alone were two times as likely to have used community-based day services as compared to those who lived with others.

Table 4.9: Logistic regression model of factors associated with use of inpatient services, QUATRO study

Potentially associated factors	*N=770*	
	Odds ratio	*95% Confidence Interval*
Treatment… …relative to no treatment	0.93	0.55, 1.56
Time 1(follow-up)… …relative to Time 0 (baseline)	0.46***	0.31, 0.68
Non-adherent… …relative to adherent	1.40	0.92, 2.15
Intervention x Non-adherence interaction	1.02	0.39, 2.69
Age (5 year increase in age)	0.99	0.90, 1.09
Females… …relative to males	0.97	0.69, 1.36
Lives alone… …relative to lives with others	0.67**	0.48, 0.94
Amsterdam (The Netherlands)… Leipzig (Germany)… Verona (Italy)... ...relative to London (UK)	1.69** 4.69*** 0.87	1.02, 2.80 2.71, 8.13 0.51, 1.46
Education – further or tertiary... ...relative to primary, secondary or general	1.05	0.74, 1.49
Not White European… …relative to White European	0.99	0.62, 1.58
Number of years on medication	0.99	0.97, 1.01
Link test p-value	0.2976	
Pearson's chi-squared test p-value	0.2997	
Hosmer-Lemeshow chi-squared test p-value	0.2087	
Likelihood ratio chi-squared p-value	0.0001	
Percent correctly classified	66.18	

* p<0.10; ** p<0.05; *** p<0.01

Table 4.10: Generalised linear model of factors associated with inpatient costs, QUATRO study

Potentially associated factors	*N=291*	
	Coefficient	*95% Confidence Interval*
Treatment… …relative to no treatment	-0.033	-0.45, 0.38
Time 1(follow-up)… …relative to Time 0 (baseline)	-0.23	-0.58, 0.13
Non-adherent… …relative to adherent	-0.092	-0.49, 0.30
Intervention x Non-adherence interaction	0.99*	-0.15, 2.13
Age – in 5 year increments	0.0051	-0.074, 0.085
Females… …relative to males	-0.20	-0.50, 0.10
Lives alone… …relative to lives with others	-0.14	-0.44, 0.16
Amsterdam (The Netherlands)… Leipzig (Germany)… Verona (Italy)... ...relative to London (UK)	1.07*** -0.24 -0.41	0.62, 1.51 -0.74, 0.27 -1.02, 0.21
Education – further or tertiary... ...relative to primary, secondary or general	0.17	-0.17, 0.50
Not White European… …relative to White European	-0.38**	-0.77, 0.0023
Number of years on medication	0.0022	-0.018, 0.022
Constant	9.93***	9.24, 10.62
Link function	Log	
Distributional family	Gamma	

* p<0.10; ** p<0.05; *** p<0.01

Table 4.11: Logistic regression model of factors associated with use of community-based day services, QUATRO study

Potentially associated factors	*N=770*	
	Odds ratio	*95% Confidence Interval*
Treatment… …relative to no treatment group	1.33	0.83, 2.12
Time 1(follow-up)… …relative to Time 0 (baseline)	1.03	0.71, 1.49
Non-adherent… …relative to adherent	0.86	0.57, 1.31
Intervention x Non-adherence interaction	0.41*	0.16, 1.11
Age (5 year increase in age)	1.04	0.95, 1.14
Females… …relative to males	1.05	0.76, 1.46
Lives alone… …relative to lives with others	2.06***	1.49, 2.83
Amsterdam (The Netherlands)… Leipzig (Germany)… Verona (Italy)... ...relative to London (UK)	0.77 0.95 1.38	0.47, 1.25 0.56, 1.61 0.84, 2.25
Education – further or tertiary... ...relative to primary, secondary or general	0.88	0.63, 1.23
Not White European… …relative to White European	1.20	0.76, 1.91
Number of years on medication	1.02*	1.00, 1.04
Link test p-value	0.4232	
Pearson's chi-squared test p-value	0.3207	
Hosmer-Lemeshow chi-squared test p-value	0.6205	
Likelihood ratio chi-squared p-value	0.0001	
Percent correctly classified	61.46	

* p<0.10; ** p<0.05; *** p<0.01

Also, the greater the number of years on medication, the greater the probability of having used community-based day services. This model correctly predicted 61% of cases and the link test suggested that the model was not misspecified. The likelihood ratio, Pearson's and Hosmer-Lemeshow test p-values suggested acceptable goodness-of-fit.

The interaction between treatment and non-adherence in this model approached statistical significance (p=0.080). If the effect of non-adherence is estimated seperately for those who received the study intervention, the odds of using community-based day services are significantly lower for those within this group who were non-adherent as compared to those who did adhere.

Among those who used community-based day services, the GLM model found that non-adherence was associated with the costs incurred. That is, community-based day service use costs were significantly lower for those deemed non-adherent as compared to those who did adhere to their medication (see Table 4.12). Additionally, women incurred less costs than men and those with a tertiary or further education incurred greater costs as compared to those without this level of education.

Again the interaction term approached significance (p=0.075) suggesting that the effect of non-adherence differed according to whether or not the study intervention was received. Separate estimation of the effect of non-adherence on community-based day service use costs for those who received the study intervention found this effect to not be significantly different from zero (p=0.424).

Graphicallly, the effects of non-adherence and the other significant variables are illustrated in Figure 4.3. Relative to the base case (male, age 45, of White European ethnicity, without tertiary or further education, resident in London, adheres to medication, lives with others, randomised to adherence education and on medication for six years), follow-up community-based day service use costs were halved if the base case was altered to be that of an individual non-adherent to medication. An increase in costs of approximately €600 was predicted if the base case was altered to be an individual living alone.

Table 4.12: Generalised linear model of factors associated with cost of community-based day services, QUATRO study

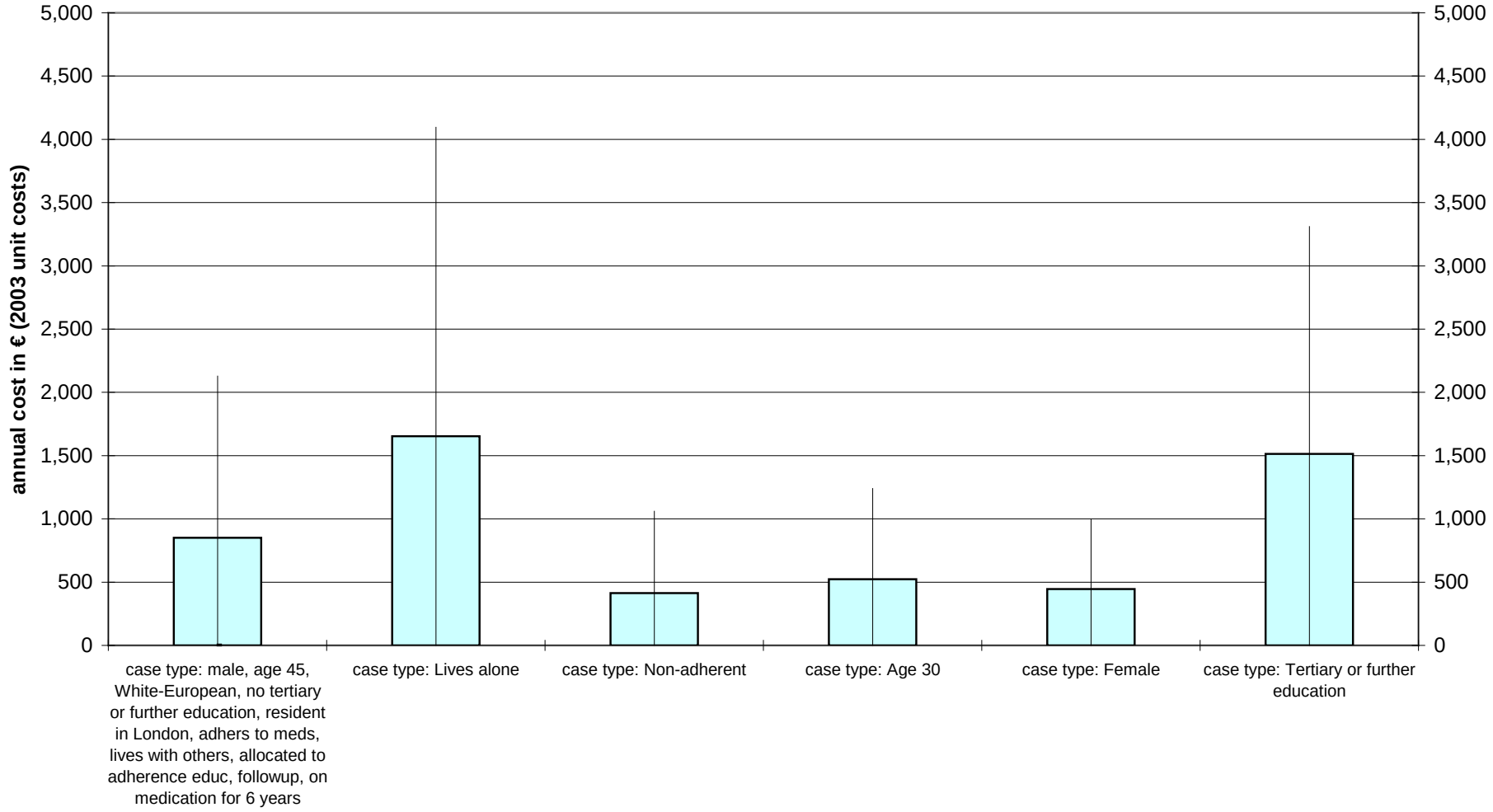
Potentially associated factors	*N=282*	
	Coefficient	*95% Confidence Interval*
Treatment… …relative to no treatment	-0.87**	-1.55, -0.18
Time 1(follow-up)… …relative to Time 0 (baseline)	-0.076	-0.65, 0.50
Non-adherent… …relative to adherent	-0.72**	-1.37, -0.078
Intervention x Non-adherence interaction	1.12*	-0.11, 2.34
Age – in 5 year increments	0.13	-0.039, 0.30
Females… …relative to males	-0.66**	-1.22, -0.11
Lives alone… …relative to lives with others	0.26	-0.31, 0.82
Amsterdam (The Netherlands)… Leipzig (Germany)… Verona (Italy)... ...relative to London (UK)	0.51 0.52 -0.36	-0.23, 1.24 -0.74, 1.78 -1.12, 0.40
Education – further or tertiary... ...relative to primary, secondary or general	0.71**	0.11, 1.32
Not White European… …relative to White European	0.016	-0.63, 0.66
Number of years on medication	-0.021	-0.052, 0.011
Constant	7.72***	6.38, 9.07
Link function	Log	
Distributional family	Gamma	

Net effect of non-adherence if adjusted is 0.44 (-0.64, 1.52)

* p<0.10; ** p<0.05; *** p<0.01

Figure 4.3

Predicted cost of community-based day services, QUATRO study



Informal care costs

The final key cost component to be analysed were informal care costs. The logistic regression model found that among individual characteristics, living with others was associated with receipt of informal care as would be expected (see Table 4.13). Those who lived alone were 30% less likely to receive informal care. The link test suggested this model was adequately specified. The model correctly classified 59% of cases. The Pearson's, Hosmer-Lemeshow and likelihood ratio test p-values all suggested adequate goodness-of-fit.

The GLM on informal care costs did not find non-adherence to be significanly associated with informal care costs amongst those who received informal care (see Table 4.14). These costs were associated with age and gender. The association with age was negative. That is, within the sample of recipients of informal care, as age increased, the informal care costs declined. With respect to the other significant effect, women had greater informal care costs than men.

Figure 4.4 graphically illustrates the impact of the significant effects on informal care receipt and costs relative to a base case. The base case chosen was the same as in Figure 4.3. That is, of a man, age 45, of White European ethnicity, without tertiary or further education, resident in London, who adheres to medication, lives with others, allocated to adherence education and on medication for six years. The model predicted the informal care costs for the base case to be €3,250. Altering the base case to that of someone who lives alone was associated with a €1,000 reduction in the predicted cost of informal care. If the characteristics of the base case are altered such that the case is of a 30 year old, the predicted costs would increase by just under €1,200. A €4,100 increase in predicted informal care costs was associated with the effect of changing the base case to that of a woman as opposed to a man.

Table 4.13: Logistic regression model of factors associated with receipt of informal care, QUATRO study

Potentially associated factors	*N=768*	
	Odds ratio	*95% Confidence Interval*
Treatment… …relative to no treatment group	0.96	0.60, 1.54
Time 1(follow-up)… …relative to Time 0 (baseline)	0.57***	0.40, 0.82
Non-adherent… …relative to adherent	1.16	0.77, 1.75
Intervention x Non-adherence interaction	1.18	0.50, 2.78
Age (5 year increase in age)	1.05	0.97, 1.15
Females… …relative to males	1.19	0.86, 1.63
Lives alone… …relative to lives with others	0.70**	0.51, 0.96
Amsterdam (The Netherlands)… Leipzig (Germany)… Verona (Italy)... ...relative to London (UK)	0.54** 1.11 0.89	0.33, 0.87 0.67, 1.84 0.55, 1.42
Education – further or tertiary... ...relative to primary, secondary or general	1.05	0.76, 1.47
Not White European… …relative to White European	0.91	0.58, 1.44
Number of years on medication	1.00	0.98, 1.02
Link test p-value	0.2414	
Pearson's chi-squared test p-value	0.3790	
Hosmer-Lemeshow chi-squared test p-value	0.6395	
Likelihood ratio chi-squared p-value	0.0001	
Percent correctly classified	58.9	

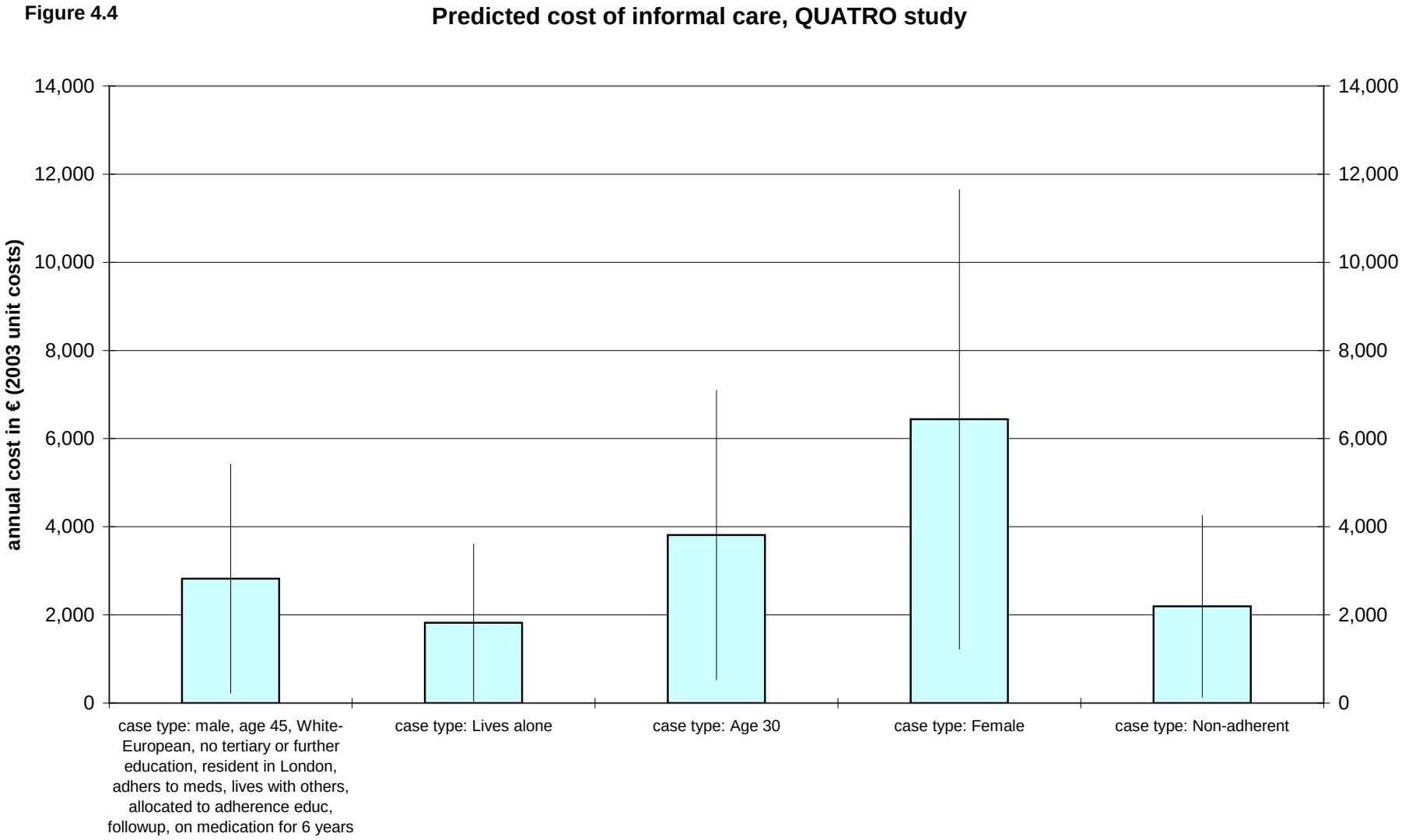
* p<0.10; ** p<0.05; *** p<0.01

Table 4.14: Generalised linear model of factors associated with cost of informal care, QUATRO study

Potentially associated factors	*N=326*	
	Coefficient	*95% Confidence Interval*
Treatment… …relative to no treatment group	-0.25	-1.03, 0.53
Time 1(follow-up)… …relative to Time 0 (baseline)	0.51*	-0.049, 1.08
Non-adherent… …relative to adherent	-0.15	-0.42, 0.13
Intervention x Non-adherence interaction	-0.018	-1.12, 1.08
Age – in 5 year increments	-0.13***	-0.21, -0.042
Females… …relative to males	0.77***	0.46, 1.07
Lives alone… …relative to lives with others	-0.19	-0.46, 0.078
Amsterdam (The Netherlands)… Leipzig (Germany)… Verona (Italy)... ...relative to London (UK)	-1.38*** -0.086 -0.10	-1.75, -1.01 -0.61, 0.43 -0.50, 0.29
Education – further or tertiary... ...relative to primary, secondary or general	0.21	-0.096, 0.51
Not White European… …relative to White European	-0.14	-0.48, 0.20
Number of years on medication	0.0062	-0.013, 0.025
Constant	9.82***	9.12, 10.51
Link function	Log	
Distributional family	Inverse Gaussian	

* p<0.10; ** p<0.05; *** p<0.01

Figure 4.4


Predicted cost of informal care, QUATRO study
annual cost in € (2003 unit costs)
14,000
12,000
10,000
8,000
6,000
4,000
2,000
0
case type: male, age 45, White-European, no tertiary or further education, resident in London, adhers to meds, lives with others, allocated to adherence educ, followup, on medication for 6 years
case type: Lives alone
case type: Age 30
case type: Female
case type: Non-adherent

4.3.6 Sensitivity analyses

Estimates from previous studies are that between 25% and 80% of schizophrenia patients do not adhere to their medication as prescribed (Battaglia 2001; Conley and Kelly 2001). Cramer and Rosenheck (1999), in a systematic review, found the mean rate of non-adherence among patients with psychoses to be 42%. The rate of non-adherence in the QUATRO study was at the low end, ranging from 11% to 49% across sites. Given that the rate of non-adherence was markedly lower in Amsterdam (11%) relative to the three other sites, sensitivity analyses were conducted to determine the effect of excluding the patients from Amsterdam to see how this would impact the study results.

In the model of societal costs, excluding the Amsterdam sample the effect of non-adherence increases but remains statistically insignificant (see Table 4.15; p=0.115). Also, as in the primary results, in the model of health and social care costs which excluded observations from Amsterdam, the effect of non-adherence did not achieve statistical significance (p=0.246). The interaction between treatment and non-adherence was statistically significant in this model at the 0.05 level. While the effect of non-adherence was not significant when the study intervention is not received, amongst recipients there was a significant positive association between non-adherence and inpatient costs (p=0.021).

The association between non-adherence and the probability of use of community-based day services differs by receipt of the study intervention when the Amsterdam sample is excluded from the analyses. When the intervention was received there was a significantly lower probability of use of these services (p=0.004). At the same time, amongst those not receiving the study intervention non-adherence was associated with significantly lower community-based day service use costs (p=0.028). These costs were not associated with non-adherence amongst recipients of the study intervention. Additionally, excluding the Amsterdam sample resulted in there being a significant negative association between non-adherence and informal care costs.

Table 4.15: Results of sensitivity analysis on effect of non-adherence on primary outcomes, QUATRO study - Excluding observations from Amsterdam [§]

	Outcome	***Coefficient***	***95% Confidence Interval***
Excluding Amsterdam sample			
Non-adherence	Health and social care costs	-0.16	-0.44, 0.11
Treatment x Non-adherence interaction		0.56	-0.17, 1.29
Non-adherence	Societal costs	-0.19	-0.43, 0.047
Treatment x Non-adherence interaction		0.57	-0.034, 1.18
Non-adherence	Inpatient visits	1.43	0.90, 2.27
Treatment x Non-adherence interaction		1.23	0.43, 3.55
Non-adherence	Inpatient costs	-0.11	-0.52, 0.31
Treatment x Non-adherence interaction		1.29**	0.13, 2.46
Non-adherence	Use of community-based day services	0.81	0.52, 1.26
Treatment x Non-adherence interaction		0.28**	0.095, 0.84
Non-adherence	Cost of community-based day services	-0.72**	-1.37, -0.078
Treatment x Non-adherence interaction		1.17*	-0.11, 2.34
Non-adherence	Use of informal care	1.21	0.78, 1.87
Treatment x Non-adherence interaction		1.17	0.47, 2.91
Non-adherence	Cost of informal care	-0.36**	-0.71, -0.015
Treatment x Non-adherence interaction		0.65	-0.43, 1.72

* p<0.10; ** p<0.05; *** p<0.01

[§]All other effects are included in these models but are not listed here.

Another sensitivity analysis was undertaken to determine the impact of the choice of threshold in the Morisky score used to determine non-adherence. Shalansky (2004) suggests using other choices of a threshold score so as to trade off between the sensitivity and positive predictive value of the scale in detecting 'true' non-adherent patients. Sensitivity analyses were conducted to determine if using a threshold score of 3 on the Morisky score to define non-adherence would have an impact on the results. That is, individuals were deemed non-adherent if they reported that in the past three months they had at some point either forgotten to take medication, were careless about taking medication, had at some point stopped taking medication once they felt better, or had at some point stopped taking medication because it made them feel worse.

Using the lower threshold level suggested that 52.8% of the sample were non-adherent at baseline. For all of the outcomes analysed the effect of non-adherence remained statistically non-significant (see Table 4.16). Thus, the higher threshold did not alter the results of the primary analyses.

4.4 Discussion

The results of the analyses set out in this chapter suggest that non-adherence does not have a significant impact on the health and social care or societal costs incurred in schizophrenia patients. This finding is not consistent with analyses in the previous chapter that looked at factors associated with use of health and social care services which included residential costs. For subsamples of the data, there was evidence of non-adherence being associated with higher inpatient costs. For some subsamples there was evidence that non-adherence was associated with lower community-based day service use costs when these costs were incurred. While the samples and settings of the PMS 1993/4 and QUATRO studies differ markedly, the results suggest that the contribution to costs of non-adherence may be relevant for some services. This is consistent with the results observed by Gilmer et al (2004). They found that while total costs were actually lower for those individuals who did not adhere to their medication, hospital costs were significantly higher for the non-adherent group.

Table 4.16: Results of sensitivity analysis on effect of non-adherence on primary outcomes, QUATRO study - Lower threshold to define non-adherence [§]

	Outcome	***Coefficient***	***95% Confidence Interval***
Lower threshold used to define non-adherence			
Non-adherence	Health and social care costs	-0.057	-0.35, 0.24
Treatment x Non-adherence interaction		0.16	-0.35, 0.67
Non-adherence	Societal costs	-0.072	-0.33, 0.18
Treatment x Non-adherence interaction		0.033	-0.44, 0.50
Non-adherence	Inpatient visits	1.14	0.78, 1.67
Treatment x Non-adherence interaction		1.23	0.55, 2.73
Non-adherence	Inpatient costs	-0.16	-0.54, 0.22
Treatment x Non-adherence interaction		0.24	-0.51, 0.99
Non-adherence	Use of community-based day services	0.83	0.56, 1.22
Treatment x Non-adherence interaction		0.65	0.31, 1.36
Non-adherence	Cost of community-based day services	-0.016	-0.77, 0.74
Treatment x Non-adherence interaction		-0.090	-1.16, 0.98
Non-adherence	Use of informal care	1.07	0.74, 1.54
Treatment x Non-adherence interaction		0.98	0.47, 2.03
Non-adherence	Cost of informal care	-0.14	-0.45, 0.17
Treatment x Non-adherence interaction		-0.78	-1.75, 0.20

* $p<0.10$; ** $p<0.05$; *** $p<0.01$

[§]All other effects are included in these models but are not listed here.

One consideration as to why non-adherence was not significant in predicting health and social care or societal costs in the QUATRO study was that the sample for this study was made up of patients deemed to be clinically unstable in the year prior to the start of the study. Indeed, a hospital inpatient stay in the year prior to the study was one of the criteria for individuals to be considered for inclusion in the study. These patients were likely to be less functional than a general schizophrenia sample. However, this was also an inclusion criterion in the study by Gilmer et al (2004) which observed no statistically significant difference in total treatment costs between adherent, partially adherent and non-adherenct individuals, but significantly higher hospitalisation costs for the non-adherent group. Relative to the 1993/4 PMS sample, when a comparable index of non-adherence was used for the QUATRO sample (Morisky score of 3 or below), the latter were, at baseline, more likely to be non-adherent and had been on medication for longer, potentially reflecting greater severity of illness. The QUATRO sample was also more ethnically diverse and had higher educational attainment, on average, as compared to the 1993/4 PMS sample.

Another consideration is whether or not the sample in the QUATRO study was large enough to detect meaningful differences in costs with sufficient power. The sample size calculation performed for this study was based on the primary clinical outcome of the main study, the SF-36 mental component summary score (Gray, Leese et al. 2006). Retrospective estimation of the power of this study for the service use outcomes (and by extension costs) is difficult as these outcomes typically have high variability leading to under estimation of power (Gray, Marshall et al. 1997). Based on the standard error observed in the analysis of health and social care costs, the sample size of the study was sufficient to observe a 44% difference in costs with 80% power. How much of a change in costs this represents depends on where on the distribution of costs it is applied. At the 10th percentile, a change of 44% is less than the difference between the 10^{th} and 5^{th} percentile. At the 90^{th} percentile, a 44% change would reflect the difference from the 90% to the 76^{th} percentile. With respect to societal costs, the sample size of the study was sufficient to observe a 38% difference in costs with 80% power.

Previous studies that have examined the relationship between non-adherence and health care costs have focussed on hospitalisation costs. Svarstad et al (2001) found non-adherers, that is those whose claims data indicated a three month gap in claims for medication, were significantly more likely to have been rehopsitalised and incurred significantly higher inpatient costs. Weiden et al (2004) observed that gaps in medication therapy, based on

prescription claims, were positively correlated with risk of hospitalisation In the PMS analysis there was a trend towards an association between inpatient visits and non-adherence being significant, but this was the case in the QUATRO analysis only for those patients who received the study intervention.

Non-adherence was associated with lower community-based day service costs (when these services were used) in the QUATRO study. In the analysis of the PMS 1993/4 sample, visits to patients by community-based health and social care professions were positively associated with non-adherence. If it is accepted that non-adherence to medication will result in resumption or exacerbation of symptoms in patients taking antipsychotics, the point of contact for non-adherent patients will depend on how long they wait before seeking health and social care help, the way services are organised in their area and the ease with which they are able to access the services they seek out. If non-adherent patients do not seek health or social care support as their symptoms increase in severity, the effects of non-adherence may be observed in the wider societal services such as the criminal justice system. My results suggest that community care professionals may be the primary source of care for non-adherent individuals who require services. Use of community-based day services appears to associated with a greater degree of acceptance of medication (based on adherence and length of time on medication).

The observed lower health and social care and societal costs experienced by those patients living alone may reflect the role that co-resident family and friends play in identifying and encouraging those individuals with schizophrenia to access the available services. However, those living alone were significantly more likely to use community-based day services. Community-based day services are the services most likely to be substituted with informal care. This suggests that informal care acts as a substitute for community-based day services but as a complement to other health and social care services. Because these effects were present after accounting for non-adherence in the model, it would indicate that the impact of co-resident family or friends was not affecting costs solely through reduced rates of non-adherence. These results were not observed in the earlier analyses of PMS data.

Also contradictory to the earlier analyses is the direction of the association between ethnicity and costs. The PMS analysis did not find a significant difference in total health and social care costs between non-Whites and Whites, though non-Whites had significantly higher inpatient

costs and were significantly less likely to use external services. Analysis of the QUATRO data indicated that sample subjects who were not White European had lower health and social care costs (at a level that approached statistical significance) and significantly lower societal costs. There was also a trend for those not White European to have incurred lower inpatient costs when inpatient services were used. More than one interpretation of these contradictory findings is possible, although further information would be required to conclude definitively. It may be that the two ethnic minority subsamples differed quite significantly in the two studies. The PMS data compared all non-Whites to Whites while the QUATRO study compared White Europeans with other ethnicities. Also, the settings of the two studies differ appreciably. The effect of ethnicity observed in a study of British patients would be expected to differ from this effect as estimated in a study including individuals from other countries. It should be noted, however, that in the QUATRO study, only the London (46.7%) and Amsterdam (56.0%) samples included ethnic minority patients. Further difference on the ethnic mix of the non-White samples could exist. Minority ethnic groups were not sampled in sufficient numbers to determine wether the mix of ethnicities were similar in the two studies. The difficulty with making conclusions regarding the impact of ethnicity is that like the PMS and QUATRO studies, few studies are sufficiently large to sample from ethnic minorities with schizophrenia in sufficient numbers.

The analysis of the PMS data identified associations between length of time on medication and the use of external services and day activity services. In the QUATRO analysis a significant positive association was found between length of time on medication and use of community-based day services. These results suggest that familiarity with medical treatment allows patients to feel more comfortable with use of community-based services. These results may also, in part, reflect greater stability in the treatment of patients over the course of their illness. That is, patients may become more able to rely on community services as opposed to inpatient or outpatient services. Another conclusion may be warranted, however, as the QUATRO study sampled unstable patients so one would expect that familiarity with medication in this group to be poor and unrepresentative of stability of their medication regime.

4.4.1 Limitations

There are several aspects of the QUATRO study that may limit the strength of the conclusions drawn from these data. Firstly, the sample in the QUATRO study was relatively small, both overall and within each site. The results may not be generalisable to the populations within each site and across sites.

The use of a multi-centre, cross-country sample has some advantages, but may also lead to problems and uncertainty. There are many challenges to such a study design as survey instruments have to be translated and in costing services uncertainty is likely given that services are delivered in different ways across sites and unit costs for services are not always available (Patel 2006). With regards to differences in unit costs across countries, a sudy by Heider et al (2009), which followed samples of schizophrenia patients in France, Germany and the UK for two years, found that while differences existed in the costs for individual services, the total adjusted costs of health services were less variable than the unit costs.

Because the Morisky scale is basing non-adherence assessment on self-reporting, it runs the risk of underestimating non-adherence. As discussed in chapter 2, however, self-assessment of non-adherence is the method most widely used in studies of schizophrenia patients (Velligan, Lam et al. 2006) and few studies corroborate self-reported adherence with pill counts or physiological data (Zygmunt, Olfson et al. 2002). More fundamentally, comparisons across studies are difficult because the definitions of what constitutes adherence, the period over which it is assessed and the sample of patients on whom it is assessed, vary widely across studies.

The QUATRO study data is also lacking information that would be beneficial in the interpretation of the nature of the relationship between non-adherence to medication in schizophrenia and service use costs. The prior analysis of PMS data adjusted for some factors that were not considered in the analysis of the QUATRO data because they were not available in the dataset. These were general health status, whether or not co-morbidity was present (based on the CIS-R score), self-reported use of illegal drugs and self-reported alcohol abuse. However, none of these factors were statistically significant in the model of total health and social care costs in the previous analyses. The PMS analysis observed an association between

drug abuse and lower costs of external service use. Unfortunately, because the QUATRO study did not collect data on illegal drug use this association could not be tested for in the current analysis.

Another important omission is data on the type of antipsychotics prescribed to the patients in the study. Without this information it is not possible to determine if certain prescribed antipsychotics are more cost inducing than others, or in fact if the general class of the antipsyhchotic, 'typical' or 'atypical' impacts on costs. Evidence to date suggests that adherence rates are similar across the different generation of antipsychotics and across different specific medications. Gilmer et al (2004) found no difference in adherence rates between those treated with the atypical antipsychotics risperidone, olanzapine and quetiapine and those treated with typical antipsychotics and refers to two other studies where similar results were found. They do not, however, compare service use costs across medications. There may be other effects of the type or class of antipsychotic prescribed that may impact on costs. For example, it could be the case that a particular medication was better than others in preventing weight gain which did not impact on adherence rates but did reduce costs incurred from illness due to the gain in weight. For this reason, it is not possible to say that had data on the type or class of drug been included in the QUATRO study, this would have had a direct impact on the interpretation of the effect of non-adherence in this study. Also, as mentioned earlier, the reason for not including the cost of treatment in the measure of costs was that is would be in effect replicating a difference in the treatment and control groups that is determined by the inclusion of a treatment effect in the model.

Finally, while longitudinal, the duration of the QUATRO study is still quite short relative to a lifetime of schizophrenia and the (probable) long-term impacts of non-adherence. That is, some of the negative impacts of non-adherence might not be observed within the one year over which patients were followed in this study or if changes in service use have occurred, these changes may persist for longer than this length of time.

Despite these limitations the analysis of the QUATRO study data was helpful in assessing the relationship between non-adherence and costs. Unlike previous literature that has tended to estimate this association using cross-sectional data, the longitudinal element of this study allows for estimates to take account of changes over time. The longitudinal nature of the

study, the robust method of assessing adherence and the detailed information on service use data made it the best available source for examining these associations.

4.5 Summary

The QUATRO study, a randomised control trial assessing the efficacy of an adherence therapy intervention in individuals with schizophrenia, provided longitudinal data from which to analyse the relationship between non-adherence and service use costs. The dataset included thorough information from which health and social care service use costs were estimated, as well as criminal justice and informal care costs. The sum of these costs was taken as an approximation of societal costs.

Non-adherence was not found to be associated with either health and social care service use costs or societal costs, but for subsamples of individuals was significantly associated with higher inpatient costs and lower community-based day service costs. The significance of non-adherence may have been underestimated as the sample was made up of clinically unstable patients. The service use patterns of these individuals may not be representative of a broader range of patients with schizophrenia. Also, the sample of the QUATRO study may not have been large enough to observe meaningful differences in costs with adequate power. Further, the duration of the QUATRO study – one year – may not have been sufficiently long to observe the long-term effects of non-adherence.

Living alone was associated with significantly lower health and social care and societal costs.This may reflect the importance of support from family and friends in the lives of people with schizophrenia in encouraging them to seek out services and providing informal care. The associations between ethnicity and a lower probability of use of community services and a greater probability of inpatient visits found in analysis of the 1993/4 PMS institutions sample were not observed in this dataset.

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Chapter 5

Associations between medication non-adherence and resource use and costs for people taking medication for depression – analysis of the Psychiatric Morbidity Survey 2000

5.1 Background

Given that some illnesses are more debilitating than others, it follows that attitudes towards medication are likely to vary widely across illnesses. Furthermore, the side effects of medications differ widely across medication types and these differences are reflected in varying rates of non-adherence to medication across different illnesses. In trying to understand the impact of non-adherence to medication on service use and service use costs in patients with schizophrenia it is important, therefore, to consider how the associations differ from those that would be observed in a different illness population. To do this, I have chosen to look at patients with another mental illness, depression.

The UK Office of National Statistics (2008) estimates that the prevalence of treated depression in the UK was 5% in 1998 and the World Health Organization estimated that major depression will carry the second highest disease burden by 2020 (Murray and Lopez 1996).

The incidence of depression is higher than that for schizophrenia although the actual medication cost per patient is lower due to the lower unit cost the of medications taken. The Health and Social Care Information Centre (2009) reported the average net ingredient cost per prescription in England in 2008 to be £34.55 for drugs used in psychosis and related disorders and £6.88 for antidepressants.

Estimates of non-adherence rates in depression are comparable to those in schizophrenia. In a study conducted in California in the US, Venturini et al (1999) retrospectively studied the pharmacy claims data of 942 patients and determined that over a six month period only 13% of patients completed an adequate course of treatment with selective serotonin reuptake inhibitors (SSRIs). Adequate treatment was defined as the average daily dose exceeding 90%

of the minimum therapeutic dose. Another US-based study, relying on automated pharmacy data and reviewing medical records, observed that among 155 patients newly prescribed antidepressants, 28% stopped their medication in the first month and by the third month 44% had stopped taking their medication (Lin, Korff et al. 1995). Cantrell et al (2006) conducted a retrospective study of patients starting treatment on SSRIs for depression or anxiety using a large US managed care database which included data for approximately 23,000 patients and observed a 57% rate of non-adherence.

The prevalence and burden of illness of depression and the non-adherence rates of patients prescribed medication for this illness are good reasons to use patients with this illness as a comparator to those with schizophrenia in assessing the impact of non-adherence to medication. Both illnesses are likely to affect a patient's insight into their illness, a factor thought to impact on non-adherence. Also, the medications for both schizophrenia and depression have significant (but different) side effects.

Side effects vary according to the type of antidepressant prescribed. Those associated with selective serotonin reuptake inhibitors are nausea, diarrhoea, agitation, headaches, loss of libido, erectile dysfunction and failure to reach orgasm. The side effects associated with tricyclic antidepressants include dry mouth, blurred vision, drowsiness, dizziness, tremors, skin rash, weight gain or loss and sexual dysfunction. Monoamine oxidase inhibitors are less likely to have associated side effects in of themselves but are associated with very adverse effects, such as heart attack and stroke, when interacted with certain foods or other medications (NICE 2007).

Here the focus is on depression, but many patients with a diagnosis of anxiety will also be prescribed anti-depressants. The primary analyses will include both groups as there is high comorbidity for anxiety and depression. Within the Psychiatric Morbidity Survey (PMS) 2000, mixed anxiety and depressive disorder was the most prevalent neurotic disorder observed (Singleton, Bumpstead et al. 2001).

Data from the PMS 2000 of adults living in private households was used to examine the factors associated with non-adherence and the relationship between non-adherence and the use of formal services and the resulting cost of these services, amongst patients taking antidepressants. The previous PMS of adults in institutions (1994) was used to examine these

associations amongst patients taking antipsychotic medication (chapter 4). While the two PMS surveys were conducted 6-7 years apart, the questionnaires used were very similar and the benefit of comparing across similar data on individual characteristics and health and social care service use outweighs limitations due to the few differences in how the data were collected.

Thus the aims of the analyses of the PMS 2000 were to estimate the rate at which treatment with medication was discontinued in patients with depression; to assess the impact of this non-adherence to depression medication on how resources were used and at what cost. These results are compared to the results observed for patients taking antipsychotic medication in the concluding chapter.

5.2 Methods

5.2.1 The Psychiatric Morbidity Survey 2000 sample

The PMS 2000 was a cross-sectional survey covering people aged 16 to 74 living in private households in England, Wales and Scotland. It was a repeat of the 1993 survey of adults living in private households with some modifications. The age range of the first survey was 18 to 65 and the PMS 2000 included measures of personality disorder and intellectual functioning (Singleton, Bumpstead et al. 2001). The PMS 2000 surveys included structural assessment and screening instruments to determine if mental disorders were present and if so, the severity of illness. Additionally, data on service use, risk factors for mental disorders and socio-demographic status were collected. A subsample of individuals was selected to undertake a second-stage interview to assess for psychosis and personality disorders. Interviews took place between March and September 2000.

The sampling frame of the survey was the postcode address file (Royal Mail 2009) and the primary sampling units were postal sectors. From the over 9000 postal sectors in Britain, 438 were selected with a probability proportional to the number of addresses within the sector. Within each postal sector, 36 addresses were selected, and if the household included 1 or

more persons aged 16 to 74 the Kish grid method (Kish 1965) was used to systematically select one person in each household to be interviewed for the survey.

The selection of individuals to include in the analyses was as follows. To minimize differences between the 1993/94 PMS and the PMS 2000, analyses were restricted to those between 16 and 65 years of age. Various data in the PMS 2000 can be used to identify patients with depression and determine the severity of the illness. A relevant sample was identified as those patients that were prescribed antidepressants at the time of the survey.

5.2.2 Variable definitions

With respect to non-adherence, as in the 1993/4 PMS surveys, the PMS 2000 survey relied on self-reported information. Patients were asked if they ever do not take the medication they have been prescribed for mental illness (and if they ever take more than the stated dose). Data was also gathered on the reason for the non-adherence and the time since the last interruption of their medication taking. The wording of these questions was identical to that used in the 1993/4 PMS surveys.

The variables included in the modelling were the same as used in the analysis of non-adherence to antipsychotics: age, sex, ethnicity, education, general level of health, illness severity, previous experience of side effects, inpatient contact for mental health reasons in the past year, self-reported drug abuse, self-reported alcohol abuse, social support, and familiarity with medication. Derived variables produced by the primary data collection team, and used in the main report, were the source of some indices used in my analyses (Singleton, Bumpstead et al. 2001). As in the 1993/4 PMS, data on ethnicity was collected in nine categories, but for the purpose of the analyses was collapsed into White and non-White due to the small number of respondents in each of the individual non-White classifications. The education variable was collapsed from five categories to three. The first category combined those with a degree, teaching, Higher National Diploma, nursing or A Level qualification. The second category includes those with GCSE or equivalent education and the third included those with no qualifications.

The index of drug dependency was the derived variable provided in the dataset (Singleton, Bumpstead et al. 2001). This variable took the value of one if the respondent reported dependency on any drug and zero if they did not. A variable indication alcohol abuse was also taken from the derived variables. This variable took a value of one, indicating a drinking problem, if the respondent had a combined score of eight or more on the ten drinking audit questions included in the survey.

Levels of general health were reported by patients on a five-point scale which was collapsed to three levels: very good/good; average; and poor/very poor as some of the original categories had relatively few observations. The wording of the question in the survey relating to general health was the same as in the earlier PMS studies though in the PMS 2000 this question was part of the SF-12 instrument. As previously, prevalence of symptoms relating to and severity of neurosis was based on results from the Revised Clinical Interview Schedule (CIS-R), a standardised instrument used to assess the prevalence and severity of symptoms in minor psychiatric disorders (Lewis, Pelosi et al. 1992). Support from an adult with whom the patient feels close was based on the question: 'How many adults who live/are staying here with you do you feel close to?'

The course of treatment for patients taking antidepressants is typically shorter than that for patients taking antipsychotics. The NICE (2007) guidelines for the treatment of depression states that:

> "Antidepressants should be continued for at least six months after remission of an episode of depression, because this greatly reduces the risk of relapse. Patients who have had two or more depressive episodes in the recent past, and who have experienced significant functional impairment during the episodes, should be advised to continue antidepressants for two years."

For this reason, consideration was given for changing the definition used to assess medication familiarity from two years, as used in the analysis of non-adherence to antipsychotics, to a period of one year for antidepressants. Examination of the PMS 2000 data suggested that a substantial proportion of patients reported taking antidepressants for 2 years of more (39.8%), so the decision was taken to use this period in defining medical familiarity.

5.2.3 Costing service use, benefits and absenteeism

The potential economic consequences of non-adherence that were analysed were the cost of health and social care services, costs to the state and the cost of time off work due to illness. This is a wider group of costs considered than in the analyses of non-adherence in antipsychotics. The additional cost outcomes were analysed because previous literature looking at the impact of non-adherence on costs in patients taking antidepressants suggested that these wider costs were substantial in this patient population.

A list of benefits included in the analysis, along with the individual health and social care services included, appears in Table 5.1. With respect to GP visits, survey respondents were asked if they had visited their GP in the past year and if these visits related to a physical or psychological problem. The number of visits in the past year was not requested. Respondents were also asked the number of times they had visited their GP in the past 2 weeks. Because the 2 weeks prior to the survey were not necessarily representative of GP service use in the past year, a decision was made to use the information on whether or not they had visited their GP in the past year. To account for the fact that the number of visits were not recorded, those that visited their GP for a physical problem were assumed to have made 2 such visits in the past year and likewise, those that reported that they had visited their GP for a psychological problem were assumed to have made 2 visits. That is, individuals who report having visited their GP for both physical and psychological problems would be assumed to have made 4 visits in the past year.

Health and social care costs were calculated by multiplying the frequency of use of each service by the estimated national average cost for the service. The unit costs were taken from the PSSRU Unit Costs of Health and Social Care for 2001 (Netten, Rees et al. 2001). These were the costs applied in costing the 1993/4 PMS surveys. The unit costs do not include qualification costs. Daily rates were applied for inpatient stays and included accommodation costs. A cost per visit was applied to A&E outpatient visits and community care services. An average length of time of one hour was assumed per visit and the unit cost relating to hourly patient contact time was used. For community mental health centre and sheltered workshop visits, the average length time of visits was estimated and an hourly unit

Table 5.1: Health and social care services and benefits included in analyses, PMS 2000

Health and social care services	GP visits	
	Hospital inpatient stays	Secure/semi-secure or special hospital unit Acute psychiatric ward Rehabilitation or long-stay ward/facility A&E department or emergency ward General medical ward
	Hospital outpatient visits	A&E department Psychiatric outpatient department
	Day activity services	Community mental health centre Day activity centre Sheltered workshop
	Community services	Community Psychiatrist Community Psychologist Community Psychiatric Nurse Community learning difficulty nurse Other nursing services Social worker Self-help/support group Home help/home care worker Outreach worker/family support
Benefits		Income support Incapacity benefit Housing benefit Severe disablement allowance Disability living allowance

cost applied. For day activity centre visits a sessional unit cost was applied with a session being either a morning, afternoon or evening.

The unit cost for each service was multiplied by the total number of visits to that service to estimate the annual cost for that service. The data were then summed to estimate total health and social care costs.

The survey asked patients to indicate which state benefits were received. The cost of each benefit was estimated from available sources. Data from the Department of Work and Pensions Resource Centre (2008) was the source for the average weekly amount of Income Support for the population under age 60 as of May 2001. This was the estimate closest to the

age range of the sample used in the analyses. This site was also the source for the average weekly amount of the Incapacity Benefit and Severe Disablement Allowance for the working age population as of May 2001. Because the earliest data available on the Disability Living Allowance benefit was May 2002, this amount was applied to the PMS 2000 rate of receipt of this benefit. These benefit amounts were multiplied by 52 to arrive at annual amounts and then summed to arrive at the total annual cost of benefits. The costs of benefits were added to health and social care costs to estimate total costs to the state. Absenteeism costs were estimated as the length of time off work for those in employment in the past year. The national annual salary was estimated from data summarised by the UK Office of National Statistics (2001). This source estimated the average weekly gross earnings for all employees. This amount was divided by five to arrive at average daily earnings. This amount was multiplied by the number of days taken off work as reported in the dataset.

5.2.4 Statistical analyses

The first primary analysis was a logistic regression model to identify the characteristics potentially related to non-adherence to medication. In this model, the outcome was the binary variable 'Was the patient adherent or non-adherent to their prescribed medication at the time of the survey'. The other main analyses determined the factors associated with the cost of health and social care services, costs to the state and the costs of absenteeism.

The methods appropriate for modelling costs were discussed in detail in chapter 2. Only a brief summary of the methods is provided here. For each outcome, if a significant proportion of the sample did not incur the cost, a two-part modelling process was undertaken (Mullahy 1998). The first part was a model to determine which, if any, of the factors were associated with incurring the cost vs. not-incurring the cost. Here logistic regression was used. The second part was a model of the costs incurred for the subsample of those patients who did incur costs. The choice of regression model was made based on the distribution of costs. If there was not significant skewness in the data, an ordinary least-squares (OLS) regression model would be appropriate. If the costs were skewed, a GLM was fitted to the data.

In each of the models with cost outcomes, different combinations of the explanatory variables were used in an attempt to take into account potential multicollinearity between non-

adherence and those factors found to be associated with non-adherence in the sample. For the logistic regression models assessment of model fit was by the link test, the Pearson's chi-squared test, the Hosmer-Lemeshow test, the likelihood ratio test and the percentage of observations correctly predicted by the model. For the GLM model, a log link function was used and the Park test was employed to determine the appropriate distribution to apply to the data.

Robust standard-errors were applied in all analyses. Factors achieving significance at the 0.05 level were deemed statistically significant. The analysis was performed using the STATA data analysis software (STATA 2008).

As in the analyses of non-adherence to antipsychotics, predicted costs were derived for hypothetical cases based on the modelling results. Again a bootstrapping algorithm, incorporating 1,000 repetitions, was used to estimate the confidence interval for predictions based on two-part models. The case types were plotted in histograms using EXCEL (Microsoft Corporation 2003) to illustrate the relative impact of changes to key variables.

5.3 Results

Initial interviews were completed of 8,800 individuals and over 600 people participated in the second stage interviews on psychosis and personality disorder (Singleton, Bumpstead et al. 2001). A total of 412 individuals in the PMS 2000 met the criteria set out for inclusion in the analyses. That is, they were prescribed an antidepressant at the time of the survey and were below the age of 65. This sample can then be further classified according to the diagnostic criteria applied in the survey. Responses to the CIS-R and an algorithm based on the ICD-10 diagnostic criteria were used (WHO 1992; Singleton, Bumpstead et al. 2001). Based on a hierarchical classification of diagnosis, 75 (18%) of the sample of individuals prescribed antidepressant medication were classified as having severe or moderate depression as their primary illness and a further 80 (19%) as having mixed anxiety and depression as their primary illness.

The average age of the sample was 44 years of age and the sample was predominately female with only one in four of the sample being male (see Table 5.2). Within the sample, 164 patients (39.8%) self-reported that they at times did not take their medication for depression as it was prescribed.

Table 5.3 presents descriptive statistics for the cost components estimated from data on health and social care service receipt, receipt of benefit and the time off work due to illness amongst those in employment. As expected, the costs were highly skewed. In all categories of costs - except GP visits - less than 50% of the sample incurred costs. Inpatient stays accounted for the greatest proportion of the health and social care costs. Community care and day activity centre costs appeared quite large on first inspection, but a closer look at the data indicated that two observations contained what appeared to be outliers.

Table 5.2: Demographic characteristics of analysis sample, PMS 2000

	Taking antidepressants and under age 65 (n=412)
Age, years (mean (s.d.))	44.4 (11.5)
Male gender (%)	26.2
Ethnicity: White (%)	97.3
Education (%)	
Completed secondary school or university	24.2
Some secondary school	35.0
No qualifications	40.8
General health (%)	
Good	17.5
Average	27.9
Poor	54.6
Moderate or severe depression (%)	18.2
Severity of neurosis: CIS-R score (mean (s.d.))	16.4 (11.7)
'Yes' responses to survey questions (%)	
Mental health hospital stay	1.2
Drug misuse	5.1
Alcohol misuse	21.3
Has adult with whom patient feels close	90.2
Two or more yrs on antidepressant medication	39.8
Self-reported non-adherence (n (%))	164 (39.8)

Table 5.3: Distribution of costs among patients taking antidepressants, PMS 2000

	Number of users	Mean	Standard Deviation	Median	Interquartile range	Min	Max
GP	394	£49	£15	£60	£30-£60	£30	£60
Outpatient	151	624	789	296	296-592	244	6,144
Inpatient	31	4,025	6,878	1,694	484-5,049	242	35,640
Community care and day activity centre	81	2,720	8,191	456	114-2,018	5	52,963
Community care and day activity centre *	79	1,484	2,465	456	103-1,833	5	14,584
Total HSC	402	1,140	4,533	60	60-420	30	55,201
Total HSC *	400	882	2,674	60	60-404	30	35,700
Benefits	209	5,687	2,750	5,441	2,825-7,001	11	12,603
Cost to the state (benefits + HSC)	406	4,057	6,104	2,646	60-7,031	30	60,594
Cost to the state (benefits + HSC) *	404	3,777	4,647	2,646	60-7,031	30	35,700
Absenteeism	97	4,617	7,564	1,196	449-3,738	75	27,287

* Excludes 2 outliers

The first outlier resulted from a recording of an average daily receipt of 11 hours of home care in the three months prior to the survey, along with two visits of 10 hours each from a nursing service and one visit of two hours with a support group. The annual cost of community services for this patient was estimated to be £50,140. The second outlier was a patient who reported receiving home help for an average of 12 hours per day in the three months prior to the survey. This patient's annual cost of community services was estimated to be £52,960. These two potential outliers were kept in the primary analyses, but sensitivity analyses estimated results for models where these two observations were excluded.

The mean annual total health and social care service use costs incurred was £1,100. This amount was substantially less than the mean annual cost of benefits which was just under £5,700. It should be noted, however, that only just over half of the sample were receiving benefits. The influence on the distribution of the two outlier cases was reflected in the large reduction in the standard deviation values when these cases were omitted. Of the total sample of 412 individuals, 185 (44.9%) were in employment. Of sample members in employment, 97 (52.4%) had at least one day off for health reasons. The mean annual cost attributable to absenteeism was approximately £4,620.

Table 5.4 presents the distribution of costs by age. The cost of benefits and absenteeism were evenly distributed across age ranges, but health and social care costs were higher among those in the middle of the age range. Health and social care costs were also higher for men than women (see Table 5.5). The cost of benefits also followed this pattern.

With respect to the covariates included in the modelling, three individuals were missing data on ethnicity; three were missing data on their educational attainment; one was missing data on drug abuse; three were missing data on alcohol misuse; and three were missing data on the social support variable. Of the 412 individuals in the sample, 406 (98.5%) had complete data. Two were missing one variable only; one was missing two variables; and three were missing five variables. Due to the fact that so few patients were missing relevant data, and that the nature of the variables that had missing values could be interpreted as possibly being related to why the values were missing (e.g. embarrassment about alcohol abuse), multiple imputation was not performed.

Table 5.4: Distribution of costs by age, PMS 2000

	N	Health and social care	Benefits	Cost to the state (benefits + HSC)	Absenteeism
16 – 24	14	£282	2,960	3,242	214
25 – 34	83	1,094	3,023	4,117	1,342
35 – 44	108	1,470	2,356	3,826	1,100
45 – 54	117	1,204	3,295	4,499	1,196
55 – 64	90	711	2,847	3,558	831

Table 5.5: Distribution of costs by sex, PMS 2000

	Health and social care	Benefits	Cost to the state (benefits + HSC)	Absenteeism
Males	1,559	4,175	5,734	1,011
Females	954	2,426	3,380	1,114

As a result of these missing values, however, the data for the six individuals without complete data were excluded from analyses as the routines to run the models exclude cases with missing values on any of the included variables. To compare the excluded individuals with those included in the analyses, Wilcoxon rank sum tests were conducted for the continuous variables and Fisher's Exact tests for the categorical variables (Fisher 1922). The Fisher's Exact test was preferred to chi-squared test because of the small number (six) of observations within the group with incomplete data.

The only variables where the six individuals without complete data differed from those with complete data were experience of side effects and the index of social support. A greater percentage of the respondents without complete data experienced side effects (33% versus 6%; p=0.046) and a smaller percentage lived with an adult with whom they felt close (33% versus 91%; p=0.026).

5.3.1 Factors associated with non-adherence to antidepressants

In a model assessing the association of patient-, medication- and environment-related factors on non-adherence to antidepressants, the effects of age, CIS-R score, length of time on medication and having experienced side effects were statistically significant (see Table 5.6). Each five-year increase in age reduced the probability of being non-adherent by 11%. Non-adherence was significantly more likely for those patients who experienced a greater prevalence or severity of symptoms (CISR score >12). A five-unit increase in the CIS-R score increased the odds of being non-adherent by 16%.

Greater familiarity with medication, based on having been prescribed anti-depressants for two years or more, was associated with 1.6 times the odds of reporting non-adherence as compared to those on medication for less than two years. Those who had experienced side effects with their antidepressant medication were over 15 times as likely to be non-adherent to this medication. The estimate of this effect was based on 23 patients who reported experiencing side effects.

The link test p-value (0.968) of the square of the predicted value suggested that the model was not misspecified. The Pearson's and Hosmer and Lemeshow chi-squared p-values (0.3131 and 0.9108 respectively) were not significant, indicating acceptable goodness-of-fit, as did the statistical significance of the likelihood ratio chi-squared test. The percentage of observations correctly predicted by the model was 68.0%.

Table 5.6: Logistic regression model of factors associated with non-adherence to antidepressants, PMS 2000

Variables	N=406	
	Odds-ratio	95% CI
Age (5 year increase in age)	0.89**	0.79, 0.99
Gender: Male (n=106)… …relative to Females (n=300)	0.71	0.42, 1.20
Education: Higher qualifications or A-levels (n=98)… O-level [2] (n=142)… …relative to below O-level qualifications (n=166)	1.14 1.33	0.64, 2.04 0.78, 2.27
Health: Average (n=114)… Poor (n=220)… …relative to good or very good (n=72)	1.24 1.22	0.62, 2.49 0.60, 2.48
Prevalence/severity of neurosis: CIS-R score [3] (five unit increase)	1.16***	1.04, 1.29
Had a hospital stay for a mental, nervous or emotional problem (n=5)… …relative to not having had hospital stay for a mental, nervous or emotional problem (n=401)	0.14	0.011, 1.69
Experienced side effects (n=23)… …relative to not experiencing side effects (n=383)	15.51***	3.45, 69.80
Ethnicity: Non-White (n=11)… …relative to White (n=395)	2.86	0.77, 10.67
Two or more years on medication (n=161)… …relative to less than 2 years on medication (n=245)	1.61**	1.01, 2.58
Lives with an adult with whom feels close (n=368)… …relative to no does not live with an adult with whom feels close (n=38)	0.84	0.39, 1.79
Reports drug abuse (n=21)… …relative to no reported drug abuse (n=385)	1.69	0.62, 4.61
Reports alcohol abuse (n=86)… …relative to no reported alcohol abuse (n=320)	1.53	0.89, 2.62
Link test p-value	0.968	
Pearson's chi-sqpared test p-value	0.3131	
Hosmer-Lemeshow chi-squared test p-value	0.9108	
Prob > LR chi-squared	0.0001	
Percent correctly classified	68.0	

* $p \leq 0.10$; ** $p \leq 0.05$; *** $p \leq 0.01$

[1]The Revised Clinical Interview Schedule (CIS-R) is used to assess minor neurotic psychiatric disorder; higher scores indicate greater prevalence or severity of symptoms.

5.3.2 Health and Social Care costs

As only ten patients did not incur any health or social care service use costs, rather than complete a two-step model for this dependent variable, these patients were included as they represented a relatively small portion of the sample (2.4%). The generalised linear model for this outcome employed a log link function and the Park test suggested a gamma distribution for this data. Health status, CIS-R score and length of time on medication were significantly associated with total health and social care costs (see Table 5.7). Those in average or poor health had higher health and social care costs than those in good health. Likewise, as the prevalence or severity of symptoms increased, higher health and social care costs were incurred. Having been on medication for two or more years was also associated with higher total health and social care costs as compared to having been on medication for less than two years. There was a trend towards non-adherence being associated with lower health and social care costs as compared to those who did adhere to their medication ($p=0.083$).

Figure 5.1 illustrates the marginal increase in cost attributable to the significant effects in the model of health and social care costs. As a starting point, the predicted costs were calculated for an arbitrary case. This initial case was for a man, age 45, White, without O-Level academic qualifications, who had a low prevalence and severity of symptoms, had average general health, who adhered to his medication, did not misuse drugs or alcohol, had social contact with an adult with whom he felt close and had been on medication for 2 or more years. The effect of altering this case to that of an individual with poor health status as opposed to the average was a £4,300 increase in predicted health and social care costs. The costs attributed to altering the case to someone who did not adhere to his medication was a £100 decrease in the predicted costs relative to the base case. The high degree of uncertainty in these estimates is reflected in the wide confidence intervals.

Table 5.7: Generalised linear model of factors associated with health and social care costs, PMS 2000

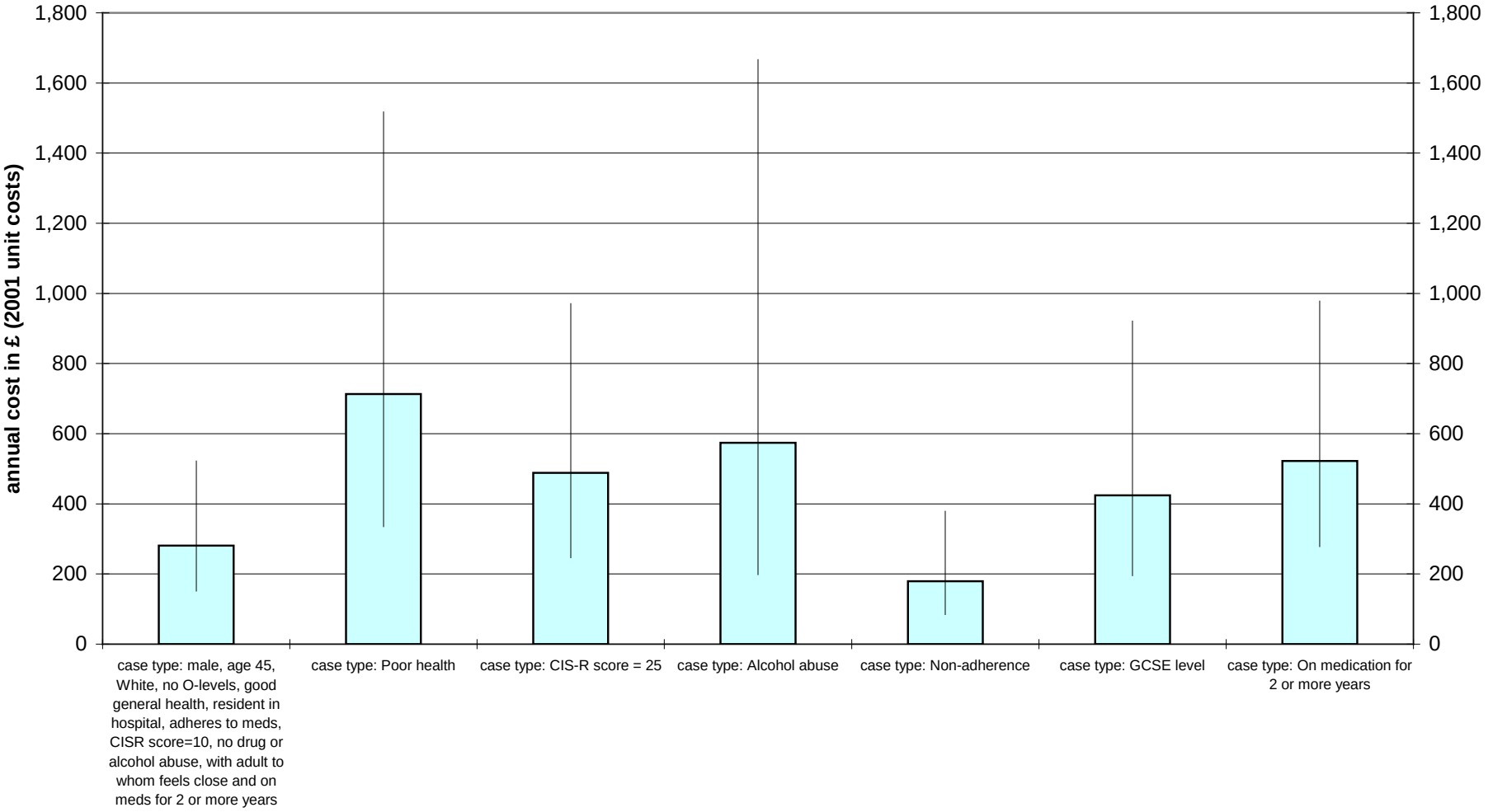
Independent variables	N=406	
	Coefficient	95% CI
Age	0.00017	-0.025, 0.026
Male (n=108)… …relative to Female (n=304)	0.19	-0.33, 0.71
Higher qualifications or A-levels (n=100)… O-levels (n=144)… …relative to below O-level qualifications (n=168)	0.49* 0.41	-0.093, 1.07 -0.20, 1.03
Non-White (n=11)… …relative to White (n=401)	-0.44	-1.54, 0.65
Average general health (n=115)… Poor general health (n=225)… …relative to good general health (n=72)	0.84*** 1.77***	0.29, 1.38 1.21, 2.33
CIS-R score [1]	0.037***	0.015, 0.059
Non-adherent (n=164)… …relative to adherent (n=248)	-0.45*	-0.96, 0.059
Lives with adult with whom feels close (n=371)… …relative to does not live with adult with whom feels close (n=41)	0.16	-0.39, 0.71
Reports illegal drug use (n=21)… …relative to non drug users (n=391)	0.053	-0.92, 1.02
Reports moderate or high alcohol dependence (n=87)… …relative to no alcohol dependence (n=325)	0.72	-0.18, 1.62
Two or more years on medication (n=164)… …relative to less than 2 years on medication (n=248)	0.62**	0.13, 1.11
Constant	4.07***	2.60, 5.54
Link function	Log	
Distributional family	Gamma	

* $p \leq 0.10$; ** $p \leq 0.05$; *** $p \leq 0.01$

[1] The Revised Clinical Interview Schedule (CIS-R) is used to assess minor neurotic psychiatric disorder. Higher scores indicate greater prevalence/severity of symptoms.

Figure 5.1

Predicted health and social care costs, PMS 2000



When the two observations thought to be potential outliers were excluded from the analysis of health and social care costs, the results were somewhat altered in that while the health status and severity of illness effects remained statistically significant, the effect of length of time on medication was no longer significant (p=0.134). In this model, non-adherence no longer approached statistical significance (p=0.275) and gender was significant (p=0.018) with males generating higher health and social care costs. When those variables found to be associated with non-adherence (age, CIS-R score, length of time on medication) were excluded from the model to take account of potential multicollinearity, there was no change in the significance of non-adherence.

5.3.3 Costs to the state

The costs of benefits paid to the patient were combined with the health and social care service use costs to arrive at costs to the state. Here, as with the previous model, a generalised linear model was estimated. In this model, a log link function was used and the Park test suggested a Poisson distribution underlying the data (see Table 5.8). As in the previous model, all cases with complete data contributed to the model estimation. Relative to those without qualifications, the respondents who achieved A-Level or university qualifications incurred lower costs to the state. There was also a significant association between general health status and these costs. As general health worsened, costs to the state increased. Similarly, as the prevalence and severity of neurosis symptoms increased, costs to the state also increased. Also, these costs were significantly higher for those who had been taking antidepressants for two or more years as compared to those who had been on medication for less than two years. The effect of non-adherence was not significant.

Table 5.8: Generalised linear model of factors associated with costs to the state (health and social care costs plus cost of benefits), PMS 2000

Independent variables	N=406	
	Coefficient	95% CI
Age	-0.014	-0.033, 0.0056
Male (n=108)… …relative to Female (n=304)	0.24	-0.078, 0.55
Higher qualifications or A-levels (n=100)… O-levels (n=144)… …relative to below O-level qualifications (n=168)	-0.59*** -0.27	-0.96, -0.22 -0.69, 0.15
Non-White (n=11)… …relative to White (n=401)	0.21	-0.35, 0.77
Average general health (n=115)… Poor general health (n=225)… …relative to good general health (n=72)	0.74** 1.29***	0.11, 1.37 0.74, 1.84
CIS-R score [1]	0.014***	0.0053, 0.024
Non-adherent (n=164)… …relative to adherent (n=248)	-0.13	-0.43, 0.17
Lives with adult with whom feels close (n=371)… …relative to does not live with adult with whom feels close (n=41)	0.31*	-0.052, 0.66
Reports illegal drug use (n=21)… …relative to non drug users (n=391)	0.034	-0.32, 0.39
Reports moderate or high alcohol dependence (n=87)… …relative to no alcohol dependence (n=325)	0.13	-0.37, 0.64
Two or more years on medication (n=164)… …relative to less than 2 years on medication (n=248)	0.40***	0.10, 0.70
Constant	7.28***	6.20, 8.37
Link function	Log	
Distributional family	Poisson	

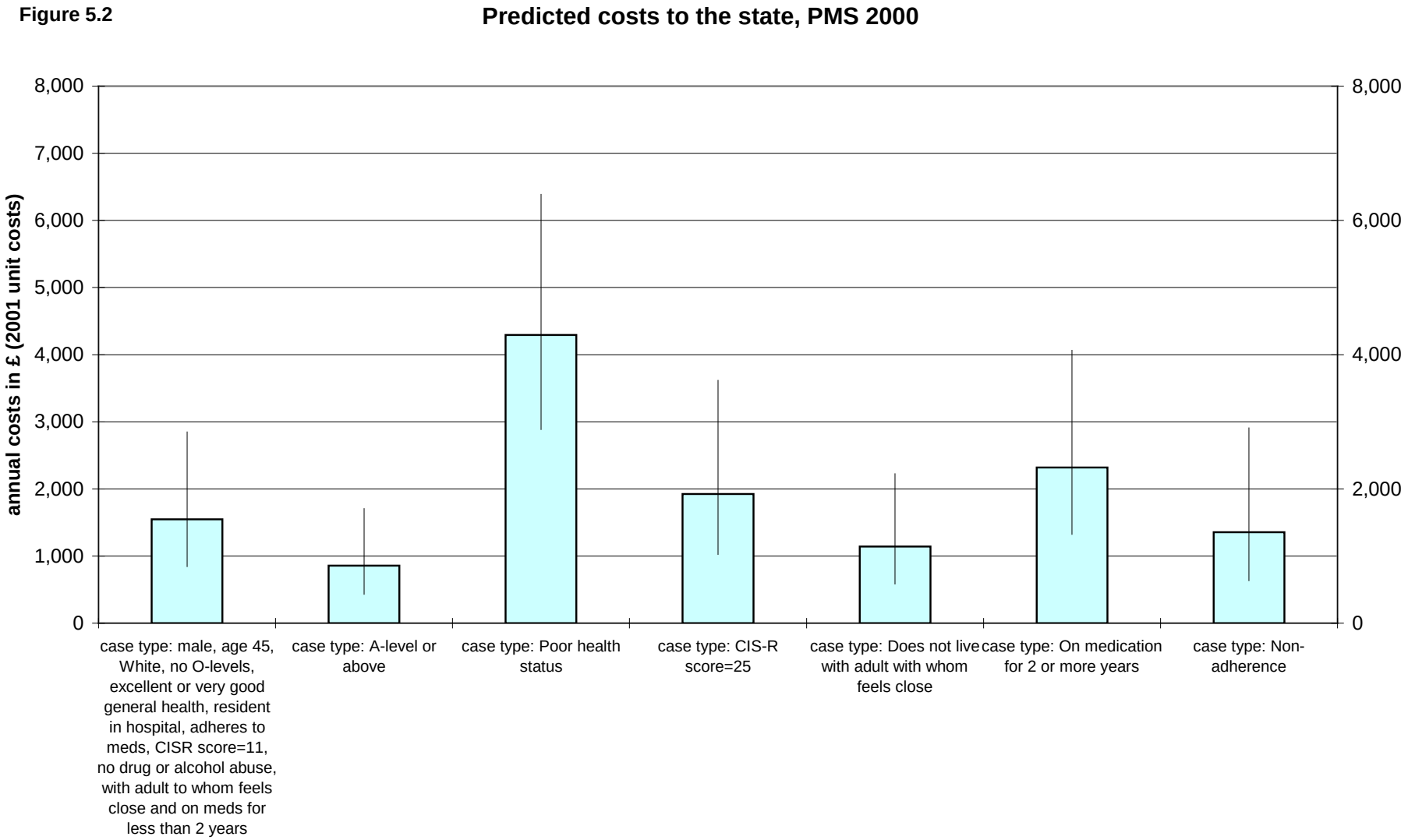
* $p \leq 0.10$; ** $p \leq 0.05$; *** $p \leq 0.01$

[1] The Revised Clinical Interview Schedule (CIS-R) is used to assess minor neurotic psychiatric disorder. Higher scores indicate greater prevalence/severity of symptoms.

Illustrations of the marginal effects of key variables appear in Figure 5.2. The initial case chosen for this model was that of a man, age 45, White, who had completed O-Levels, had low prevalence and severity of symptoms, was in very good general health, adhered to his antidepressant medication, did not misuse drugs or alcohol, had social contact with an adult with whom he felt close and was on antidepressants for less than two years. For this case the predicted costs to the state were £1,550. The effect of changing the case to a non-adherent patient reduced predicted costs by just under £200. The largest increase in the predicted costs occurred if the case was changed to someone in poor health or on medication for two or more years. In these cases the predicted costs increase by £2,750 and £770 respectively. If the highest level of educational qualifications was assumed, predicted costs to the state were £690 less than those predicted for the initial reference case.

When the model was run without the two potential outliers, the effects of education, health status, illness severity and length of time on medication remained statistically significant. In this model, age and gender were also significantly associated with costs to the state. As the age of patients increased the costs incurred by the state decreased. Also, the costs to the state were higher for male patients than for female patients. As in the analysis of health and social care costs, the potential multicollinearity between non-adherence and age, CIS-R score and length of time on medication did not appreciably alter the significance of non-adherence.

Figure 5.2


Predicted costs to the state, PMS 2000
annual costs in £ (2001 unit costs)
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0
case type: male, age 45, White, no O-levels, excellent or very good general health, resident in hospital, adheres to meds, CISR score=11, no drug or alcohol abuse, with adult to whom feels close and on meds for less than 2 years
case type: A-level or above
case type: Poor health status
case type: CIS-R score=25
case type: Does not live with adult with whom feels close
case type: On medication for 2 or more years
case type: Non-adherence

5.3.4 Cost of absenteeism

The final outcome of interest was absenteeism costs. A sample of 185 respondents reported being in employment in the last year and were asked the number of days that they had been away from work due to ill health. The effect of ethnicity could not be included in the logistic regression analysis as the three ethnic minority respondents who reported being in employment in the last year had all experienced days off work due to ill health. That is, the index of the effect of being from an ethnic minority perfectly predicted having time off work. Thus it was not possible for the model to estimate the effect of ethnicity on whether or not someone had taken experienced time off work and the effect of ethnicity was excluded in this model.

As would be expected, the model found that poor health was associated with having incurred absenteeism costs (see Table 5.9). Those with poor health were nearly five times as likely to have taken time off work for ill health as compared to those in excellent or good health. There was also a trend towards those with O-Level academic qualifications to have greater odds of having had a period of absence from work as compared to those without O-Level qualifications (p=0.065).

The link test p-value (0.0.566) suggested the model was satisfactorily specified. The Pearson's and Hosmer and Lemeshow chi-squared p-values (0.2586 and 0.2435 respectively) were not significant, indicating acceptable goodness of fit. The statistical significance of the likelihood ratio chi-squared test suggested that the model fit the data adequately (p=0.0195). The percentage of observations correctly predicted by the model was 64.3%.

In the GLM run on those people with depression who did report days missed from work (n=99), the cost of absenteeism was modelled with a log link function and the Park test suggested a gamma distribution. Age, health status, severity of illness, alcohol abuse and non-adherence were all statistically significantly associated with the cost of absenteeism (see Table 5.10).

Table 5.9: Logistic regression model on factors associated with having incurred absenteeism costs (amongst those in work), PMS 2000

Independent variables	N=182	
	Odds Ratio (of using services)	95% CI
Age (5 year increase in age)	1.10	0.93, 1.29
Male (n=108)… …relative to Female (n=304)	0.75	0.32, 1.76
Higher qualifications or A-levels (n=62)… O-levels (n=72)… …relative to below O-level qualifications (n=48)	1.31 2.18*	0.56, 3.05 0.95, 4.97
Non-White (n=0)… …relative to White (n=182)	-	-
Average general health (n=72)… Poor general health (n=55)… …relative to good general health (n=55)	1.30 4.86***	0.59, 2.86 1.83, 12.93
Prevalence/severity of neurosis: CIS-R score [1] (five unit increase)	0.97	0.80, 1.18
Non-adherent (n=68)… …relative to adherent (n=114)	1.69	0.85, 3.39
Lives with adult with whom feels close (n=164)… …relative to does not live with adult with whom feels close (n=18)	0.68	0.20, 2.30
Reports illegal drug use (n=7)… …relative to non drug users (n=175)	1.13	0.21, 5.96
Reports moderate or high alcohol dependence (n=43)… …relative to no alcohol dependence (n=139)	1.12	0.51, 2.44
Two or more years on medication (n=47)… …relative to less than 2 years on medication (n=135)	0.60	0.28, 1.31
Link test p-value	0.566	
Pearson's chi-sqpared test p-value	0.2586	
Hosmer-Lemeshow chi-squared test p-value	0.2435	
Likelihood ration chi-squared p-value	0.0195	
Percent correctly classified	64.3%	

* $p \leq 0.10$; ** $p \leq 0.05$; *** $p \leq 0.01$

[1] The Revised Clinical Interview Schedule (CIS-R) is used to assess minor neurotic psychiatric disorder. Higher scores indicate greater prevalence/severity of symptoms.

Table 5.10: Generalised linear model of factors associated with cost of absenteeism, PMS 2000

Independent variables	N=99	
	Coefficient	95% CI
Age	0.055***	0.022, 0.088
Male (n=18)… …relative to Female (n=81)	0.056	-0.50, 0.61
Higher qualifications or A-levels (n=33)… O-levels (n=44)… …relative to below O-level qualifications (n=22)	-0.057 0.39	-0.69, 0.58 -0.24, 1.03
Non-White (n=3)… …relative to White (n=96)	-0.64*	-1.35, 0.075
Average general health (n=35)… Poor general health (n=41)… …relative to good general health (n=23)	0.43 1.42***	-0.26, 1.12 0.62, 2.22
CIS-R score [1]	0.043***	0.010, 0.077
Non-adherent (n=43)… …relative to adherent (n=56)	-0.57**	-1.05, -0.089
Lives with adult with whom feels close (n=88)... …relative to does not live with adult with whom feels close (n=11)	0.24	-0.69, 1.16
Reports illegal drug use (n=4)… …relative to non drug users (n=95)	-0.16	-1.08, 0.76
Reports moderate or high alcohol dependence (n=25)... …relative to no alcohol dependence (n=74)	-0.61**	-1.23, -0.0031
Two or more years on medication (n=22)… …relative to less than two years on medication (n=77)	-0.66*	-1.37, 0.045
Constant	4.62***	2.76, 6.48
Link function	Log	
Distributional family	Gamma	

* p≤0.10; ** p≤0.05; *** p≤ 0.01

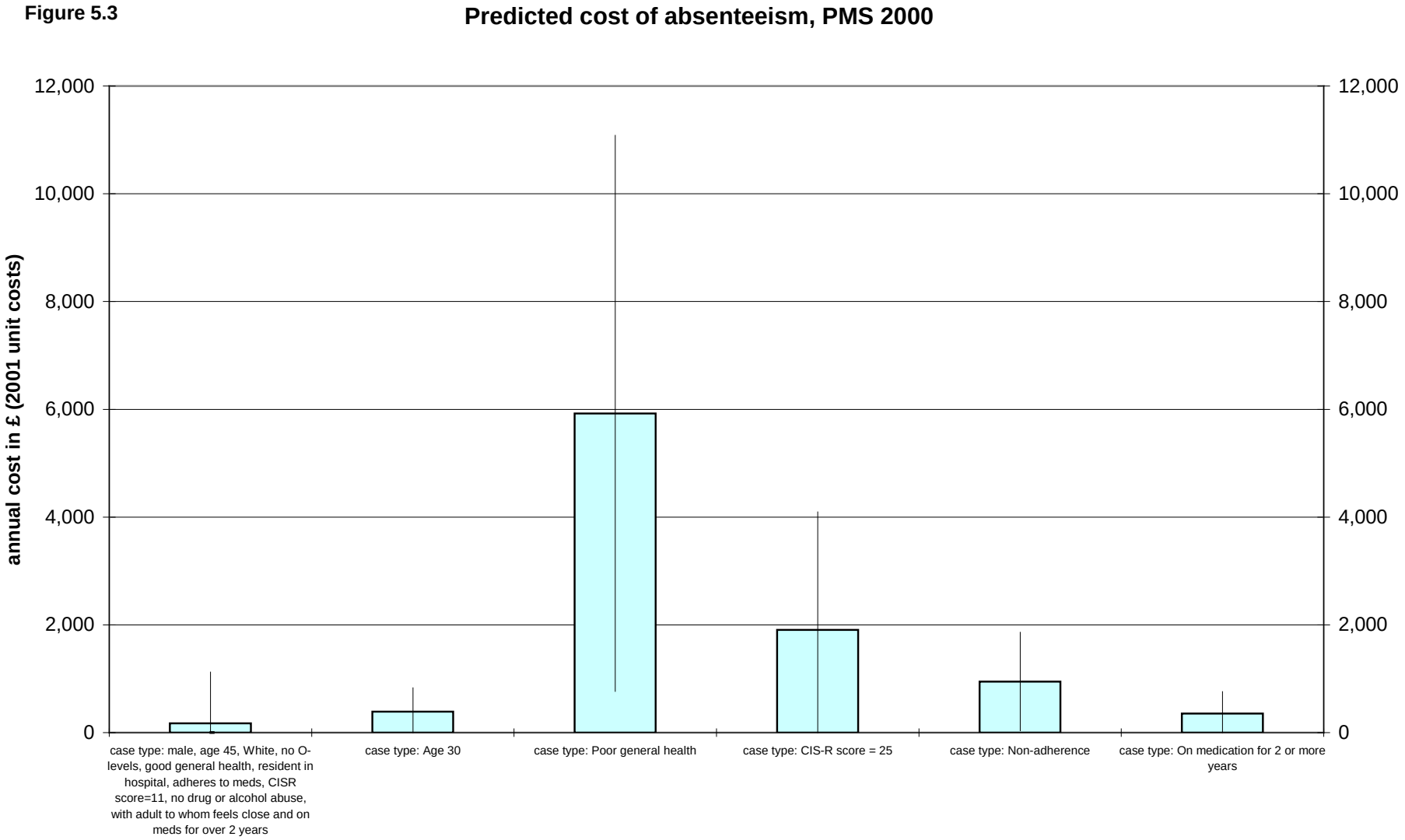
[1] The Revised Clinical Interview Schedule (CIS-R) is used to assess minor neurotic psychiatric disorder. Higher scores indicate greater prevalence/severity of symptoms.

Absenteeism costs increased as patients got older and were significantly greater for those in poor health as compared to those in good health. The cost of absenteeism were lower for those who reported alcohol abuse as compared to those who did not report alcohol abuse, and individuals who reported being non-adherent to medication also had lower absenteeism costs. There was also a positive relationship between absenteeism costs and the CIS-R score (which reflects prevalence and severity of symptoms).

The effects of ethnicity and length of time on medication approached statistical significance ($p=0.079$ and $p=0.066$ respectively). The trend was for individuals from an ethnic minority to have lower absenteeism costs than their White counterparts. Recall, however, that this effect was estimated based on only three ethnic minority respondents. Those on medication for two or more years had lower absenteeism costs as compared to those on medication for less than two years.

Figure 5.3 illustrates the impact of the significant effects on absenteeism costs. Due to the relatively small sample size, the bootstrap algorithm did not converge to a solution in several repetitions when the full list of variable was included in the models. To get around this problem, the models were altered to include only those variables found to be statistically significant in either the logistic regression on whether or not days off were taken due to ill health and the GLM on the amount of costs attributable to these lost days. A hypothetical base case of a 45 year old individual, without O-Level qualifications, in average health, who had a score of 10 on the CIS-R, adhered to medication and had been prescribed antidepressants for less than two years. The impact of relatively few observations on which to base the estimates of absenteeism costs was reflected in the wide confidence intervals around each of the estimates. As would be expected, poor general health had the greatest impact on increasing absenteeism costs. Relatively poor mental health, reflected in prevalence and severity of neurotic symptoms also significantly increased absenteeism costs. There was a trend for non-adherence to increase the probability that a respondent had days off work due to ill health but to decrease the frequency of days off, and thus costs. On balance, non-adherence increased the estimate of annual absenteeism costs by over £750, suggesting that those in work are likely to feel good and able to cope without taking their medication.

Figure 5.3


Predicted cost of absenteeism, PMS 2000
annual cost in £ (2001 unit costs)
12,000
10,000
8,000
6,000
4,000
2,000
0
case type: male, age 45, White, no O-levels, good general health, resident in hospital, adheres to meds, CISR score=11, no drug or alcohol abuse, with adult to whom feels close and on meds for over 2 years
case type: Age 30
case type: Poor general health
case type: CIS-R score = 25
case type: Non-adherence
case type: On medication for 2 or more years

5.4 Discussion

The analysis of the PMS 2000 data, by incorporating costs associated with receipt of benefits and absenteeism costs, provides a very broad overview of the observable direct and indirect costs incurred by individuals prescribed antidepressant medication. It is noteworthy that the costs of both benefits and absenteeism were substantial and amongst those who incurred these costs, far outweigh health and social care service use costs. Few factors were found to be associated with non-adherence in the data. Analyses of costs found that non-adherence was significantly associated with absenteeism costs only, and this association was negative. The analyses also determined that two outliers have a substantial impact on some of the findings. There was a trend towards non-adherence being negatively associated with health and social care service use costs, but this trend disappeared when the potential outlier values were excluded from the analyses.

5.4.1 Rate of non-adherence in individuals taking antidepressants

The rate of non-adherence in this study was 40%. It was very difficult to determine from the literature if consistent estimates of the rate of non-adherence could be observed due to difference in settings, patient populations and methods use to assess adherence. A review of the literature on non-adherence in patients taking anti-depressants identified several large studies with widely differing rates of non-adherence for the time periods under study. Rates of non-adherence ranged from 35% to 70%. Within the PMS 2000 sample a large proportion of those taking antidepressants were judged to have mild or moderate depression. This contrasts with some of the previous studies in this area that have focussed on patients with severe depression or had a greater proportion of patients with severe depression. This may partly explain the relatively low prevalence of non-adherence to antidepressants in the PMS 2000 data as compared to other studies.

A large (n=4,312) US-based study estimated non-adherence rates for newly diagnosed, privately insured patients with major depression (Akincigil, Bowblis et al. 2007). The sample consisted of members of the general population who were enrolees in a large health care organisation operating in north-eastern US states. Assessment of adherence was based on

pharmacy refill records for the period from January 2003 to January 2005. The non-adherence rates were 49% in the first 16 weeks of treatment, increasing to 58% by week 33.

Cantrell et al (2006) studied adherence to SSRI medication using medical and pharmacy claims data from a managed care database in the US covering 30 health plans and holding records of over 25 million persons across the US. This study included data for nearly 23,000 individuals newly prescribed SSRIs during the period of July 2001 to June 2002. The 6-month adherence rate was approximately 57% and this estimate was consistent across varying methods of assessing adherence: length of therapy, medication possession ratio and a combination of the two. Olfson et al (2006) in a nationally representative US sample observed a 42% rate of non-adherence in the initial 30 days of treatment with an antidepressant and a 72% rate of non-adherence after 90 days.

Pampallona et al (2002), in a review of non-adherence in depression identified 32 studies published between 1973 and 1999. Fifty percent of these were US-based studies, ten were conducted in the UK, three in Canada and three in continental Europe. In total, these studies included over 10,000 patients, all of whom were diagnosed with depression. The range of rates of non-adherence was between 30% and 97% with a median of 63%. The methods used to assess adherence varied across studies.

A literature review on medication compliance in psychiatric treatment identified ten articles which assess the rate of compliance for patients taking medication for depression (Cramer and Rosenheck 1998). The review was based on a MEDLINE search of literature published between 1975 and 1996. The methods of assessing adherence in these studies were primarily pill counts and lithium blood levels supplemented by patient interviews. Two of the articles included in the review were meta-analyses. The review found that the mean rate of non-adherence across the studies was 37% and ranged from 10% to 60%.

Using quite strict criteria to assess a patient as adherent (a combination of identifying detectable serum levels of study medication at all follow-up assessments, self-reported assurance and attendance at scheduled visits), a Swedish study found that 60% of patients with major depressive disorder were non-adherent to their medication in the first 24 weeks of treatment (von Knorring, Akerblad et al. 2006).

A small (n=107) UK-based cross-sectional study found the rate of self-reported non-adherence to medication to be 35% for a sample of patients diagnosed with depression (Byng, Bury et al. 2007), while in a US sample of older patients with depression (based on secondary analysis of a prospective cohort study of participants from the (US) National Institute of Mental Health Clinical Research Center for the Study of Depression in Later Life), where self-reporting was used to asses non-adherence, approximately 28% of patients taking antidepressants reported being non-adherent in their medication taking (Bosworth, Voils et al. 2008). The results of this study, along with the analyses of the PMS 2000, support the view that self-reported non-adherence rates will be lower than if more invasive methods are used in assessment. As discussed in chapter 4, however, in a large-population survey, all methods other than self-reporting would be extremely difficult to implement. The two studies above which based non-adherence rates on large populations were both US studies that retrospectively analysed claims data for large managed care organisations.

5.4.2 Factors associated with non-adherence

My analysis observed a very strong association between the experience of side effects and non-adherence to antidepressants. This association was not surprising given the range of side effects known to affect those prescribed antidepressants as detailed in the introduction to this chapter.

In the literature reported in the previous section, rates of non-adherence to antidepressants were observed to increase over time. Just as the duration of a study is likely to impact on the rate of non-adherence, it may also influence results of analysis of the factors associated with non-adherence. Aikens et al (2005) postulate that in the period after commencing taking an antidepressant, non-adherence is related to the side effects and the perception that the medication prescribed is ineffective. In the longer-term non-adherence is likely to result from patients judging that they no longer need the medication or becoming less willing to continue tolerating previously acceptable side effects (e.g. sexual dysfunction) (Aikens, Nease et al. 2005). Note, however, that for this theory to hold, patients must distinguish between what are intolerable side effects in the short and longer term. If this theory is true, it would explain the higher rates of non-adherence observed in the literature above which sampled newly diagnosed patients prescribed antidepressants for the first time.

Several empirical studies in the literature examine the associations between non-adherence and patient-, medication- and environment-related factors. A search of the literature found two review studies, although neither was a structured or systematic review. In the first, Nemeroff (2003) identified severe side effects/adverse events such as severe daytime sleepiness, anxiety and nausea to be consistently significant contributors to non-adherence in patients taking antidepressants. The method by which the studies cited in this review were identified was not stated by the author.

The other review was a narrative review by Mitchell (2006)[4]. The author discusses the literature in support of, and opposing, the hypothesis that adherence behaviour is a form of self-medication. The method to identify the included studies is not stated. Key determinants of non-adherence for patients taking antidepressants, based on observed trends in the literature, were perceptions of stigma, concern about drugs, feeling better and side effects.

Olfson et al (2006), using data from the US Medical Expenditure Panel Survey for 1996-2001, observed associations between non-adherence to antidepressants and Hispanic ethnicity, lower educational attainment and low family income. They also observed that among patients who continued on antidepressant medication beyond the first 30 days, those treated with SSRIs were more likely to adhere to their medication than those treated with tricyclic antidepressants or other older antidepressants.

The study by Akincigil et al (2007), described above, found that non-adherence was associated with younger age, alcohol or substance abuse, comorbid cardiovascular/metabolic conditions, use of older generation antidepressants and residence in lower-income neighbourhoods.

In another US study conducted between December 1999 and May 2000, Bull et al (2002) surveyed people with major depression or depressive disorder who had recently started to take an SSRI antidepressant. In this study, patients were asked in a questionnaire if they had

[4] A narrative review summarises primary studies from which conclusions may be interpreted. Results have a qualitative rather than a quantitative meaning. Kirkevold, M. (1997). "Integrative nursing research - an important strategy to further the development of nursing science and practice." Journal of Advanced Nursing **25**: 977-984, Campbell Collaboration. (2001). "Campbell Collaboration guidelines." Retrieved February 14, 2006, from www.campbellcollaboration.org..

discontinued treatment. Thus, the outcome was a more severe interruption of medication taking beyond non-adherence. The authors found that communication about adverse events, regular visits to a physician, lack of experience of adverse events and being married significantly reduced the probability of discontinuing SSRI medication in the first 3 months.

In a small US-based study of patients prescribed antidepressants for greater than 11-weeks (defined as being in a maintenance phase of medication treatment) adherence was assessed with two forms of self-reported information (Aikens, Nease et al. 2005). Firstly, the first three items from the Brief Medication Questionnaire were used to measure the percentage of their medication adhered to in the preceding two weeks. Secondly, general adherence was assessed using the Morisky scale. This study found that a composite score that takes into account the relative weight of perceptions about the necessity of medication and the concerns about medication, derived from the Beliefs About Medication scale, was found to be statistically significantly associated with non-adherence in multivariate regression analyses that accounted for depression severity, treatment duration and social desirability bias (the tendency to answer questionnaires in the socially acceptable direction).

Loh et al (2007) conducted a survey in Germany of general practitioners and patients with depression in which they collected data at baseline and after six to eight weeks to, among other things, determine if patient participation in decision-making was associated with treatment adherence. Adherence was assessed based on response to a question put to both the GP's and the patients at the six to eight week visits, asking them to rate adherence on a 5-point scale. Using structured equation modelling, the authors concluded that an association between self-reported adherence and patient participation in shared treatment decision-making did exist. This result was observed after accounting for the severity of the patients' depression.

5.4.3 Association between non-adherence and service use and costs

Few studies were identified which analysed the associations between non-adherence to antidepressants and service use and the costs associated with service use. Cantrell et al (2006) used claims data from a large US health plan database to conduct such a study. Patients were recipients of at least one prescription for an SSRI between July 2001 and June 2002. The

authors produced three indices of non-adherence: one based on the medication possession ratio (MPR), another based on the length of therapy (LOT), and a third that combined MPR and LOT data. The results were that patients judged to be adherent to their medication incurred lower medical costs (this did not include prescribing costs). The difference in medical costs between adherent and non-adherent patients was approximately $450. When the cost of medication was included, the difference between adherent and non-adherent patients was not statistically significant.

von Knorring et al (2006), in an analysis conducted in Sweden between June 1999 and February 2003, costed health services and time off work due to illness in patients with major depression. In this study, patients were deemed to be adherent if they had detectable serum levels of medication, self-reported that they had taken medication as prescribed, and attended scheduled visits. The authors did not observe any differences in total costs incurred after two years between adherent and non-adherent patients. Inpatient costs were significantly higher for non-adherent patients. The average total cost per patient over the 2 years of the study was just under €39,000. Indirect costs were estimated at just below €34,000.

In a large study using pharmacy and medical claims data from a pharmacy benefit and medical management company in the US, adherence was defined as having 70% or greater supply of pills supplied over a 180 day follow-up period and the economic outcomes analysed were pharmacy cost charges, medical charges (depression and non-depression related physician, emergency room, hospital, laboratory and any other medical charges) and total healthcare (combined pharmacy and medical) charges (White, Vanderplas et al. 2003). Non-adherence was found to be associated with significantly lower medical charges as compared to adherent patients, though total healthcare charges were not significantly different between adherent and non-adherent patients. The difference in total medical costs for the follow-up period was approximately US$1,300.

Apart from the von Knorring work, few previous studies have assessed associations between non-adherence to antidepressants and non-health care costs. No studies were identified which used costs to the state as an outcome in assessing the potential impact of non-adherence. It could be argued that there is no theoretical basis for hypothesising that non-adherence would impact on costs to the state, but given that non-medical costs incurred by individuals with depression often greatly exceed their medical costs, it is helpful to contextualise the impact of

non-adherence from the wider perspective of costs to the state. Layard et al (2007) estimated that the average, per person, economic savings to the UK Exchequer of treating patients with depression and/or anxiety in reduced incapacity benefit, income support, housing benefit, council tax benefit and recovered employment taxes would be three times the medical costs saved. Similarly, Bosmans et al (2007), in a cost-effectiveness analysis of a pharmacy based coaching programme to improve adherence to antidepressants, estimated that the average indirect costs of absenteeism for the non-intervention group were €2,249 while the direct medical costs for this sample were €711. The data for this study were collected in 2000 and 2001, with costs adjusted to 2002 values.

5.4.4 Other factors associated with service use and costs

Amongst the other factors assessed in the models, those found to be significantly associated with health and social care costs were related to the severity of illness. Self-reported poor health, higher CIS-R scores and greater length of time on medication were all significantly associated with these costs. Similarly, poorer health was, as would be expected, associated with higher absenteeism costs. Older individuals also incurred higher absenteeism costs, perhaps reflecting the fact that having been in the workforce for longer, they would have higher incomes than younger individuals and would thus have higher costs associated with time off work. This is consistent with the fact that the probability of having time off work is not significantly associated with age. Alcohol abuse was associated with lower absenteeism costs among those who took time off work but not the probability of taking time off work. This suggests that those individuals with moderate to high alcohol intake returned to work more quickly after time off.

5.4.5 Limitations

There were some limitations associated with using the PMS 2000 dataset for the analyses undertaken as this survey was not designed specifically to address the questions being asked in my analyses. These were much the same as discussed in chapter 4 in relation to the 1993/4 PMS surveys: the inability to incorporate some potentially important factors that relate to

non-adherence, the fact that the data was cross-sectional and the resulting possibility that non-adherence may be endogenous.

As discussed in chapter 3, the source of endogeneity may be simultaneity or omitted variable bias. The inclusion of an index of medication familiarity reduced the likelihood of omitted variable bias as it is served as a proxy for the unobserved effects of the attitudes to medication and the patient's insight into their illness. The potential for simultaneity between service use and non-adherence is arguably greater in the 2000 PMS sample of individuals taking antidepressants than in the 1993/4 PMS sample of individuals prescribed antipsychotics; this is because the overall pattern of service use suggested that the main health and social care services used by the antidepressants sample were outpatient and community services. It is in these services, which are usually regular contacts between patients and health providers, where reminders and encouragement of adherence are more likely (as compared to inpatient visits). Services that offer reminders and encouragement regarding medication taking, will however, have the effect of improving adherence, and would bias down the observed effect of non-adherence in the models.

The theoretical models of non-adherence suggest key factors such as a patient's attitude to their illness and their medication are key to understanding non-adherence. With respect to the data being cross-sectional, as with patients diagnosed with schizophrenia, the nature of the associations between illness, non-adherence and service use cannot be fully understood without being able to assess causality. For patients taking antidepressants the potential exists for their illness to impact on the ways in which they perceive medication and thus whether on not they adhere, while at the same time non-adherence is likely to make symptoms worse and thus may impact on the severity of illness which may in turn impact on the use of services. Previous studies have attempted to assess the impact of depression on adherence to medication (DiMatteo, Lepper et al. 2000; Wing, Phelan et al. 2002).

The analysis of the impact of non-adherence on the cost of absenteeism was compromised by not being able to identify whether all time off work was directly related to an individual's illness for which antidepressants were prescribed. In the survey, respondents were asked to report the number of days off work for all health- related reasons. It should be noted, however, that it has been shown that depression can trigger the onset of physical health issues

(Carroll, Cassidy et al. 2004). Thus it cannot be ruled out that while some health service use may not appear to be related to depression, this may in fact be the case.

A further limitation pertains to the analysis of the cost of absenteeism. Absenteeism was taken as proxy of lost productivity, but the current literature suggests that estimates of lost productivity should also incorporate presenteeism. Sanderson and Andrews (2006) define presenteeism as 'lost productivity arising from attending work while unwell'. These costs could not be captured from the PMS 2000 data.

Donohue and Pincus (2007) conducted a literature review based on searches of MEDLINE and EMBASE between 1990 and July 2005 to assess whether the costs of depression treatment are offset by gains in worker productivity and/or reductions in other healthcare spending. Among their key findings are that suicide-related costs made up 6% of total societal costs of depression in 2000, that depression affected educational attainment, which lowers earning potential and that in addition to absenteeism, significant costs can be attributed to presenteeism – reduced productivity at work. The authors cite data from a study by Greenberg et al (2003) which estimated suicide-related costs of patients with depression in the US in 2000 to be US$5,450million and presenteeism costs to be US$15,295million. As a percentage of total costs (direct health care, suicide-related and all workplace-related costs), presenteeism accounted for 18.4% of costs. Greenberg et al (2003) estimated suicide-related costs using a human capital framework based on the total number of suicides by age and gender in 2000, with the present value of lost lifetime earnings estimated assuming 60% of suicides were attributable to depression. They estimated presenteeism by assuming that 20% of time at work while suffering from a depression episode resulted in lost productivity.

Finally, my analyses does not account for differences between antidepressant medications or between the classes of antidepressants. There is evidence that antidepressants differ in their effects on adherence to medication (MacGillivray, Arroll et al. 2003), presenteeism (Greener and Guest 2005) and total medical costs of treatment (Sheehan, Eaddy et al. 2005).

The PMS 2000 was not designed to answer specific questions regarding patient behaviours and service use, but rather as a nationally representative survey of psychiatric morbidity in the British population. It uniquely offered a snapshot of the British household population and the relative prevalence and severity of mental illnesses. The PMS 2000 and the 1993/1994 PMS

surveys, taken together, offer comparable data from similar samples. The analyses undertaken sought to make use of these data, as best possible, to assess the associations between non-adherence, patient-, treatment- and environment-related factors and a range of cost outcomes. As in the previous empirical chapters, robust statistical methods were used, increasing confidence in the associations reported.

5.5 Summary

The rate of non-adherence to antidepressants observed in my analysis of the PMS 2000 data was towards the low end of the range reported in the literature. This may be due to the assessment of non-adherence in the PMS relying on self-reported information, the smaller proportion of severely depressed and newly diagnosed patients in the sample relative to samples in previous literature. The relatively low rate of non-adherence observed may also reflect a bias for people who do not take their medication also not wanting to participate in surveys.

An association was observed between greater prevalence or severity of symptoms and non-adherence in the data. My results were consistent with the literature in finding a strong association between the experience of side effects and non-adherence to antidepressants. The literature also supports the finding that a positive association existed between length of time on medication and the probability of non-adherence. The literature suggests some potential reasons for this finding: that patients perceive that they no longer need medication or that they want to avoid side effects.

Non-adherence to medication did not appear to be strongly associated with health and social care costs or, more widely, costs to the state amongst patients taking antidepressants. For those in work there was a trend towards non-adherence increasing the probability of having had to take time off from work due to ill health but the actual number of days missed were lower amongst non-adherent individuals. Few other studies have assessed the impact of non-adherence on either health, social care or state costs of absenteeism costs. Some of these studies observe medical costs to be higher for non-adherent patients, although other results suggest a weak or opposite association.

Chapter 6
Discussion and Conclusions

6.1 Discussion of findings

The aim of this thesis was to identify those factors associated with non-adherence to antipsychotic medication and to determine the extent to which non-adherence was associated with service use costs incurred by individuals taking antipsychotics. The findings for this patient population were compared to those from a sample of individuals taking antidepressants to determine if the previously observed relationships were present in another patient group.

6.1.1 Factors associated with non-adherence

In relation to factors associated with non-adherence, my hypotheses were that where non-adherence to antipsychotic medication was driven by attitudinal factors, severity of illness and insight would be key factors, and where non-adherence was driven by external factors, social support, drug and/or alcohol abuse and the experience of side effects would be significant.

Analysis of the 1993/4 PMS institutions sample indicated that non-adherence was associated with the type of institution the individual was in, their age, level of education, severity of illness, whether or not they had an alcohol abuse problem, whether or not they had had a recent inpatient stay and whether or not they experienced medication side effects. Individuals who were in residential care homes, supervised housing, group homes or hostels were more than twice as likely to not adhere to their antipsychotics as those in hospital. The association between age and the probability of non-adherence was negative. That is, within the sample, as age increased, the probability of non-adherence decreased. Those individuals who had higher education or A-level educational qualifications were more likely to not adhere as compared to those with the lowest level of educational attainment. Individuals whose illness was deemed more severe based on the presence and severity of neurosis, those that had recent inpatient stays, those who reported moderate or high alcohol dependency and those who reported

experiencing side effects were all more likely to not adhere to their medication. The significance of a recent inpatient stay was also observed in secondary analysis of the 1993/4 PMS household and homeless samples.

These findings were difficult to compare with previous research in this area because of inconsistency in methodologies across studies. In particular, the reviewed studies differed widely in the methods used to assess non-adherence, the factors considered and the length of time over which individuals were followed. Despite these differences, some consistent findings emerged which were also observed in my analyses. Among patient-related factors, age, level of education and illness severity were significantly associated with non-adherence in other studies. Additionally, several studies observed an association between substance abuse and non-adherence, though in some studies this was an association with illegal drug misuse as opposed to alcohol, the latter being the association observed in my analysis. The most consistent finding across this literature was the association between the experience of side effects and non-adherence.

The effects of age, severity of illness and experience of side effects were also observed as significantly associated to non-adherence in analysis of individuals taking antidepressants in the PMS 2000. These findings were broadly consistent with results from other studies. Significant associations between non-adherence and socioeconomic factors, ethnicity and substance abuse have also been reported in the literature (Olfson, Marcus et al. 2006; Akincigil, Bowblis et al. 2007). In my analyses of the 1993-4 and 2000 PMS (chapters 3 and 5), the effects associated with non-adherence in both samples were consistent in the direction of their association. This suggests that these individual-level factors are important to medication taking behaviour across mental illnesses.

Some differences between the results do emerge, however. Neither an individual's level of education, nor alcohol abuse (or substance abuse more widely) had a significant impact on non-adherence to antidepressants in the analysis of the PMS 2000, although these effects were found to be significant in other studies of individuals prescribed antidepressants. In the case of the effect of having had a recent inpatient stay, in the sample of individuals taking antidepressants this was associated with a greater likelihood to adhere to their medication as compared to the sample of individuals taking antipsychotics where it was associated with greater likelihood of non-adherence. Note, however, that the finding in the sample of those

taking antidepressants is based on a very small number of recent inpatients. Also, length of time on medication was significantly associated with non-adherence to antidepressants but not with non-adherence to antipsychotics.

Where differences in the two sets of results occur, they suggest that there are particular aspects of the illness of psychosis or of antipsychotic medication that determine that certain factors influence medication taking behaviour in a way that differs from what occurs in patients taking antidepressants. For example, if it is assumed that individuals with higher educational attainment taking antipsychotics are more inclined to not take their medication because of the degree to which it inhibits their ability to function intellectually, at a level they feel they are capable of, this negative aspect does not appear to be associated with taking antidepressants.

The significance of an inpatient stay on non-adherence to antipsychotics but not to antidepressants is likely due to the relative severity of illness in the samples studied. In the 1993/4 PMS, approximately 15% of those included in the analysis sample had had an inpatient stay as compared to less than 2% of the sample of individuals taking antidepressant in the PMS 2000. If the rates of hospitalisation were similar in the two samples and having had an inpatient stay were still found to be significantly associated with non-adherence in the sample taking antipsychotics but not in the sample taking antidepressants, it would then be warranted to conclude that some aspect of the effects of acute illness warranting hospitalisation affects the subsequent medication taking behaviour of individuals with schizophrenia more that individuals with depression (e.g. disruption of therapeutic alliance).

The rate of alcohol abuse was higher in those prescribed antidepressants in the PMS 2000 compared to those prescribed antipsychotics in the 1993/4 PMS, but the effect of alcohol misuse was found to be associated with non-adherence in the latter group only. It is not obvious why alcohol abuse or substance abuse would be associated with non-adherence in one group of patients and not the other. The effect of alcohol or substance abuse was found to be associated with non-adherence to antidepressants by Akincigil et al (2007).

These results support some of my hypothesis and not others. Severity of illness, alcohol abuse and the experience of side effects were found to be associated with non-adherence to antipsychotic medication. Other factors hypothesised to be significant – the patient's level of

insight (proxied by their length of time on medication) and social support - were not found to be significant.

To gain further understanding of the findings from the empirical results it is also relevant to see how well they relate to theoretical models that attempt to describe medication taking behaviour. These models were reviewed in Chapter 1. Typically, theoretical models developed to understand medication taking behaviours focus on preventative behaviours and the behaviours relating to the initiation of treatment rather than the maintenance phase of treatment, which is the focus of my analysis. Despite this, my findings, and those of the literature looking at factors associated with non-adherence in individuals taking antipsychotics support some of the models reviewed.

Perhaps the most often cited theoretical model for explaining medication taking behaviour is the Health Belief Model (HBM). This model suggests health behaviours are determined by the interaction of personal beliefs and perceived susceptibility, severity, benefits and barriers of the behaviour. Budd et al (1996) conducted a study of the impact of the HBM in schizophrenia patients in Wales comparing 20 patients who had presented for, and accepted, depot antipsychotic medication at all scheduled appointments over the year prior to the study (compliers) with 20 patients who had failed to attend and/or accept medication for one-third or more of all scheduled appointments over the same period (non-compliers). The constructs of the HBM were evaluated using a Health Beliefs Questionnaire (Champion 1984; Pan and Tantam 1989). The authors found scores on the susceptibility subscale had the greatest discriminatory power in distinguishing compliers from non-compliers. Scores on the severity and benefits subscales were significant in distinguishing between the two groups when tested in separate analyses, but were not significant when added to a model that already contained the susceptibility subscale.

The concept of susceptibility is consistent with the assumption that those with higher educational attainment are more likely not to adhere because they perceive the effects of the medication act as a barrier to functioning at a level they feel they are capable of. More highly educated individuals may also feel less susceptible to the consequences of non-adherence. The Self-Medication Hypothesis is, like the concept of susceptibility in the Health Belief Model, supported by the significance of educational attainment if one assumes that the more educated an individual is, the more likely they are to perceive that they have a good understanding of

their illness and do not need to take medication. The Self-Medication Hypothesis suggests that individuals intentionally and rationally decide to start, adjust or stop prescribed medication according to perceived health needs based the information they are given and their understanding of their condition (Mitchell 2007). It may be the case that more educated individuals are inclined to rationalise not taking their medication and for this to be an intentional choice.

With respect to severity of illness, it is likely to be the case that, across illnesses, individuals whose symptoms are less severe will exhibit greater internal locus of control at the initial stage of treatment. That is, less severe symptoms may allow them to make the connection between taking medication and relieving symptoms. However, individuals experiencing more severe symptoms, particularly in psychotic illness where diminished cognitive function is one of the potential symptoms, may find it more difficult to perceive that they have the power, through adherence, to relieve symptoms. Where internal locus of control does not exist, patients may benefit from identifying their physicians as an external locus of control. This may account for the finding in the literature that a positive therapeutic alliance between patients and their physicians improves adherence in patients taking antipsychotics (Weiss, Smith et al. 2002; Rittmannsberger, Pachinger et al. 2004; McCann, Boardman et al. 2008).

The Self-Regulatory Model of illness does not point to specific patient-, medication- or environment-related factors being related to non-adherence in patients taking antipsychotics, but does reflect the likely dynamic nature of medication taking behaviour present in individuals taking this medication. It proposes a dynamic flow between the three stages of self-regulation – representation of the illness, development and implementation of a plan to cope with the illness and evaluation of the coping mechanism. Perhaps the most likely representation of this model in empirical findings is the significance of side effects. An individual in the stage of evaluating their coping mechanism (taking the medication), on experiencing side effects, may reflect that their coping mechanism is ineffective and become non-adherent to seek to develop a new plan for coping with their symptoms.

Interpretations of the applicability of empirical findings to the available theoretical models is difficult but may be enhanced by qualitative research methods. Using concept mapping, Kikkert et al (2006) identified five themes that encompass the factors that affect adherence: medication efficacy, external factors (such as patient support and therapeutic alliance),

insight, side effects and attitudes towards medication. The authors point out that the importance placed on each of these factors may differ substantionally between patients, carers and health professions. I will return to this point in my discussion of the implications of my findings for research.

6.1.2 The association between non-adherence and service use costs

The main hypothesis of my thesis was that non-adherence to medication in individuals taking antipsychotics, in addition to its impacts on clinical outcomes, is likely to lead to higher service use and costs. This hypothesis was put forward by researchers previously. Gilmer et al (2004) suggested that awareness and acknowledgement of the high service use costs that can be attributed to non-adherence in patients with schizophrenia might act as an incentive to locate resources to improve adherence in patients with this illness.

My empirical findings support this hypothesis for some key health and social care services. In a nationally representative sample of patients taking antipsychotics, non-adherence was associated with greater likelihood of use of community-based health and social care professionals. Also, a trend towards significance was observed between non-adherence and the use of inpatient services and the total cost of health and social care services. Additional analysis of a randomised control trial sample observed no significant association between non-adherence and either health and social care or societal costs, but a significant association between non-adherence and lower community-based day service costs. The sample size for this study was chosen based on having adequate power to observe meaningful differences on the clinical outcomes and as such, may have been under-powered in relation to measuring differences in costs.

My analyses also suggest that the relationships between non-adherence and service use and costs are specific to individuals taking antipsychotics and are likely to vary substantially for individuals taking other medications. My analysis of the PMS 2000 found a trend towards non-adherence being associated with lower health and social care service use costs in individuals taking antidepressants. There was a trend for non-adherence to be associated with absence from work in this group, although the costs attributed to time off work were significantly lower amongst those who did not adhere to their medication.

To date, few other studies have empirically modelled the effect of non-adherence on costs across a wide range of services. Previous studies have found an association between non-adherence to antipsychotics and hospitalisations and their related costs (Weiden and Olfson 1995; Svarstad, Shireman et al. 2001; Weiden, Kozma et al. 2004). These studies have observed a significant association between non-adherence and inpatient visits and their costs, confirming the trend observed in my analysis of the 1993/4 PMS. Loosbrock et al (2003) observed an association between non-adherence and total health care costs; however Eaddy et al (2005) did not observe this association although they did observe inpatient costs to be higher amongst individuals deemed partially compliant with their medication as compared to those who were overly compliant. Note that Eaddy et al (2005) included only inpatient, outpatient and physician costs in their definition of total costs.

Only two studies were identified that assessed the relationship between non-adherence and service use and costs in patients taking antidepressants. von Knorring et al (2006) found an association between non-adherence and inpatient costs, and White et al (2003) observed an association with medical charges (physician, emergency room, hospital, laboratory and any other medical charges) but not with total health care costs. As I did, von Knorring et al (2006) looked at absenteeism costs in their analysis and also did not observe a difference in these costs by adherence status.

My findings and previous literature suggest that non-adherence is associated with service use in individuals taking antipsychotics in a way that is different from patients with another mental illness. In particular, there was some evidence that inpatient and community-based services were more burdened by non-adherence than other services. Increased total health and social care costs associated with non-adherence were observed in the literature and while not conclusively supported by my analysis, there is a trend towards this observation as well in my analysis of the 1993/4 PMS. Further analysis in this area is warranted to corroborate these findings. Analysis of societal cost data suggests no differences in these costs by adherence status. It is the case, however, that my analysis and that of von Knorring et al (2006) only looked at a limited portion of the indirect costs associated with schizophrenia.

Putting these results in context, there are certain aspects of the illness of schizophrenia that may impact on the strength of my findings and findings from the literature. There is an issue

that some individuals go untreated. Data from the 2000 PMS booster sample of individuals living in private households suggests that a substantial number of individuals who potentially have psychosis go untreated. Brugha et al (2005) found that of adults interviewed in 1993 and found to probably have functional psychosis, only 34% were prescribed medication for their psychosis. Data from the PMS 2000 found that this rate had increased to 57% in 2000 (Brugha, Bebbington et al. 2004). This suggests that a large proportion of individuals with psychosis, many of whom will likely have schizophrenia, are untreated and in all probability will make demands on health, social care or other services. If some of these individuals go untreated because of difficulties adhering to medication, the estimated costs associated with non-adherence obtained by survey individuals who are taking medication will underestimate these costs.

Another issue is the difficulty associated with obtaining data on homeless individuals. The 1993/4 PMS included a survey of the homeless population and while non-adherence was not associated with total health and social care costs within this group (based on a very simple analysis), the sample was very small, and more importantly, the lack of service use in a homeless population may reflect unmet need.

A third issue that may impact upon the results is that the nature of sampling for surveys may mean that those individuals that are less likely to adhere to medication are also less likely to participate in a survey if approached to do so. All of these factors suggest that findings from empirical analysis are likely to underestimate the service use and costs associated with non-adherence to antipsychotics.

6.1.3 Other factors associated with service use and costs in patients taking antipsychotics

Of the other factors included in the modelling of service use and costs, none were found to be significant in both the 1993/4 PMS and QUATRO study analyses. Higher severity of symptoms was associated with higher external services (i.e. community-based visits by health and social care professionals), while longer length of time on medication was associated with greater probability of use of community-based day services. Length of time on medication in the QUATRO study is difficult to interpret because the sample was chosen from patients with

an unstable illness, but may relate to severity of illness which was not included in the QUATRO analyses.

The finding that non-White respondents in the 1993/4 PMS were less likely to use external services but, on average, had a greater number of inpatient visits was not confirmed by the QUATRO analyses. In the latter study, non-White European respondents were no more likely to use inpatient services than White Europeans and incurred lower inpatient costs when inpatient visits occurred. The fact that the QUATRO study sampled across countries makes it unlikely that commonalities in the patterns of service use by ethnic minority individuals would be observed.

The theoretical models presented in chapter 1 describe the current understanding of medication-taking decision-making, but to the extent that these theories can be thought of more broadly to describe decisions on all aspects of an individual's health, they offer insight into the potential pattern for non-White individuals to forgo health and social care services in the community with the apparent impact of requiring inpatient services when their mental well-being deteriorates. This pattern of decision-making about when to access services is consistent with the Health Belief Model. It suggests that non-White individuals may have different views as to the benefits of community-based health and social care services and perceive there to be barriers to accessing these services. Other research in this area also supports this application of the Health Belief Model, identifying perception of illness severity, reliance on informal support networks, a lack of trust and the perception that the providers of community psychiatric care lack cultural awareness and understanding as key reasons why non-White individuals are less likely to access community-based services (National Centre for Social Research 2002; The Sainsbury Centre for Mental Health 2002; National Institute for Mental Health in England 2003).

Severity of illness appeared to be strongly associated with total health and social care costs in individuals taking antidepressants. This was not the case in the analysis of patients taking antipsychotics identified in the 1993/4 PMS which included an index to represent this effect.

6.2 Limitations

The analyses conducted in this thesis rely on the best available data on a cross-section of individuals taking medication for whom information was collected on adherence to medication and use of health, social care and other services. As this was secondary analysis, it is important to note that none of these data were collected for this purpose directly and as such, have some limitations with respect to addressing my particular research questions. The discussion above identifies some aspects of the samples that may have made it more difficult to observe consistent results.

None of the datasets contained information on all of the factors found to be potentially associated with non-adherence in a review of the literature. With respect to the analysis of non-adherence to antipsychotics, the 1993/4 PMS and QUATRO samples differed in their settings. Had consistent results been observed across the two samples the results could be deemed more generalisable. However, the differences in the samples make it less likely to observe consistent results.

The fact that prescribing patterns are constantly changing imposes a further limitation on these analyses. These changes may have an impact on the nature of the relationship between previously observed factors affecting adherence and the relationship between non-adherence and costs. Despite these limitations, however, it is my feeling that this thesis provides important information on these relationships.

6.3 Policy Implications

My research has implications for policies that relate to patients, the health care system and future research in this area. I will first discuss the policies affecting individual patients, and then implications for the wider health care system.

6.3.1 Implications for patients

The empirical analyses within this thesis have important implications for patients. They illustrate that for a nationally representative sample, the rate of non-adherence was in line with those estimated in the literature from local studies and reviews. Given the rates at which patients report not adhering to their medication, there is a significant shortfall in the clinical benefits that could be available to patients.

Factors associated with non-adherence in my analyses are consistent with some of the previous findings within the literature. These results aid in corroborating previous findings, with the benefit that the analyses include data drawn from a nationally representative study. Also, by comparing the results for non-adherence to antipsychotics with those of non-adherence to antidepressants, for a similar population, the analyses shed light on which of the factors associated with non-adherence are particular to patients prescribed antipsychotics. That is, in addition to those factors that are likely to be associated with non-adherence across illnesses, such as the experience of side effects, there are those factors, such as substance abuse, that are more likely to be associated with non-adherence in patients experiencing psychosis. This information could potentially be used to help clinical staff to identify those patients most likely to benefit from interventions to improve adherence in patients taking antipsychotics, and to ensure that potential interventions are designed and delivered in such a way as to be targeted at those individuals most at risk of not adhering to their medication.

A range of interventions have been developed to improve medication adherence in patients with schizophrenia. These are primarily psychosocial interventions such as educational approaches, skills training, group therapy, family interventions, cognitive treatments, behavioural modification techniques or some combination of these (Byerly, Nakonezny et al. 2007). The evidence to date, while not entirely consistent, suggests that those interventions that are intensive, supportive, have a problem-solving element and include the family members of patients are most effective in improving adherence. Hudson et al (2008) found that in a trial of a practical, patient-tailored intervention to identify and develop strategies to overcome barriers to medication adherence, patients who received the intervention were less likely to be non-adherent at the 6-month study assessment. Note, however, that evidence in my results, and other literature, throw up the likely challenge of intervening with difficult-to-

reach populations such as the homeless and those with a dependency on illegal drugs. For example, a focus on family-involvement strategies to improve adherence would not address the needs of homeless individuals. The availability of long-acting injectable antipsychotic medications does, however, allow physicians to identify those patients not attending appointments and therefore not receiving their medication. Depot antipsychotic medication has become an option for treating difficult-to-reach patients.

My analyses did not estimate adherence rates for the range of antipsychotic drugs, as the datasets used did not identify the particular medication prescribed for each individual. Were this information available, it would be possible to determine to what extent non-adherence rates, and the factors related to adherence, differed by medication. A study by Gianfrancesco et al (2006) observed that in a comparison of antipsychotics on rates of adherence, where adherence was measured by medication possession ratio, use of the atypical antipsychotic quetiapine was associated with better adherence than use of two other atypical antipsychotics – risperidone and olanzapine.

6.3.2 Implications for the health care system

The current National Institute of Clinical Excellence guidance (NICE 2009) on treatment for patients with schizophrenia calls for medication choices to be made collaboratively by the person using services and healthcare professionals after the person using services has been informed of the benefits and side-effects of each drug and has had a chance to discuss this information. The guidance also calls for the views of carers to be considered if the service user agrees, and for the use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs to be discussed so that the service user is aware that these will possibly interfere with the therapeutic effects of prescribed medication and psychological treatments. Specific guidance on treating patients from ethnic minorities was also provided. The current guidance is a revision of guidance published in 2002 which recommended atypical antipsychotics as the first-choice for pharmacological treatment (NICE 2002).

The new guidance, therefore, addresses some key factors found to be associated with non-adherence as corroborated by my findings, in particular, emphasising the role of carers and family members in successful management of the illness, the potentially adverse impact that

illicit drug use can have on therapeutic effects and issues around service provision to individuals from ethnic minorities.

My findings confirmed the importance of carers and family members and suggest that the guidance could go further to address the needs of those individuals who live alone and/or are not in contact with family members. With respect to individuals with schizophrenia from ethnic minorities, it is highly likely that the observed pattern of service use which substitutes inpatient visits for community-based services reflects the fact that these individuals are only accessing services when their illness has progressed to become more severe. Further analysis is warranted to determine if the changes in the guidelines in England have the desired effect of eliminating patterns of service use that appear to be based on an individual's ethnicity.

The NICE guidance refers explicitly to non-adherence in recommending that service users are made aware of the high risk of relapse if they discontinue their medication and that depot injectable antipsychotic medication should be offered to people with schizophrenia when avoiding non-adherence is a clinical priority.

The guidance recommend that the psychological therapy and psychosocial interventions that should be offered to people with schizophrenia are cognitive behavioural therapy, family intervention (where families live with or are in close contact with the service user) and art therapy. These interventions are recommended on the basis that they are beneficial in reducing symptoms, risk of relapse or rehospitalisation or improve the quality of life of people with schizophrenia, as opposed to the specific consideration of improving adherence. However, while their impact on adherence was not the primary consideration, it is possible that they may improve adherence. The one intervention assessed by NICE that was specifically designed to improve adherence was not recommended on the grounds that trials of its clinical effectiveness did not consistently show improvement in adherence as a result of the intervention. Counselling and supportive psychotherapy and social skills training were also not recommended.

The results presented in my thesis suggest that the impact of non-adherence varied across the types of services used by individuals with schizophrenia. These results were not consistent, however, across the two studies assessing service use costs in individuals prescribed antipsychotics. Analysis of a sample of individuals taking antidepressants suggested that the

cost implications of non-adherence were not significant in this group of service users. Thus while adherence interventions may not be generally beneficial across illnesses, they have the potential to be beneficial for people taking antipsychotics.

If further evidence supported the finding that use of community-based services was associated with non-adherence, then encouraging health professionals working in this sector to provide information and practical tools to help individuals adhere to their medication may have the best outcomes for reducing non-adherence rates. As an example, Gray et al (2004) observed that medication management training given to community mental health nurses was effective in improving adherence in patients with schizophrenia.

Some common results do exist when hospital and outpatient services are contrasted with community services. In both studies, having social support was associated with an increased probability of having had an inpatient stay. This may be interpreted as evidence for the importance of monitoring individuals in secondary care without social support so as to ensure that the signs of symptom severity requiring an inpatient stay are adequately monitored. Alternatively, this result may reflect the need for community services to better support those living with individuals with schizophrenia. Another consistent finding was the significance of medication familiarity, as indexed by length of time on medication, in association with the use of community services. This suggests the need for newly diagnosed patients to be encouraged to access these services.

6.3.3 Implications for research

Having analysed data as to the factors associated with non-adherence, I believe that it would be beneficial to have a better understanding of the reasons behind the medication taking behaviour of individuals. This information would be helpful for assessing theoretical models to explain non-adherence to medication. There have been some qualitative research on the reasons individuals with schizophrenia give for not taking their medication. Löffler et al (2003) conducted a survey in Leipzig in Germany of schizophrenia patients receiving inpatient, day care or outpatient treatment. The patients were asked for their reasons for compliance and non-compliance with medication using the Rating of Medication Influences (ROMI) scale (Weiden, Rapkin et al. 1994). The reasons most often given were to avoid side-

effects of medication, no perceived benefit of the medication and lack of insight into the necessity of medication. Similar findings were observed in a study by Rosa et al (2005) in Brazil who interviewed outpatients diagnosed with schizophrenia.

Löffler et al (2003) went further and assessed the correlation between patient-related factors and responses given regarding reasons for non-adherence. Men were significantly less likely to report fear of stigmatisation as a reason for non-adherence, older patients were less likely to consider distress from side effects as a cause for non-adherence and patients with more severe symptoms were more likely to give denial of the illness and a fear of stigma as reasons for non-adherence. Also, patients who had had an inpatient stay in the previous six months were more likely to report that lack of recovery or improvement was a reason for non-adherence. These results suggest that the Health Belief Model is relevant to explaining the underlying reasons for non-adherence in individuals taking antipsychotics. The authors of this study also found that the subjective reasons for non-adherence were stable over time (Löffler, Killian et al. 2003).

Pound et al (2005) used meta-ethnography to synthesis qualitative research into the experiences of individuals with regards to their medicine taking. Reviewing studies from 1992 to 2001, they found two qualitative studies of individuals taking antipsychotics, both of which suggested that individuals weigh up the positives and negatives of their medication when making decisions on how they take medicines (Rogers, Day et al. 1998; Usher 2001). The benefits reported were reduced symptoms, improved ability to deal with symptoms and reduced risk of relapse. These were weighed up against physical and psychological adverse effects and the stigma and discrimination associated with taking antipsychotics. The studies also found that people taking antipsychotics felt pressure from relatives and health professions to take their medication and that adherence was necessary for them to be tolerated in their communities. Pound et al (2005) concluded that individuals are generally reluctant to take medicine and prefer to minimise medicine intake; the authors suggest that the focus of improving medication taking behaviour should be on developing safer medicines. Weiden (2007) makes a similar suggestion by pointing out that non-adherence may be brought about for some patients by a lack of efficacy of their medication, which exacerbates symptoms which in turn interfere with an individual's medication taking behaviour.

The theoretical models of medication taking behaviour are of benefit to the extent that they can be used in allowing individuals with schizophrenia and their health professionals to work towards making their illness more manageable. While theoretical approaches are of value for understanding an individual patient's medication-taking behaviour, the constraints of clinical practice mean that it may be difficult to assess the theoretical underpinnings of non-adherence at an individual level and make it difficult to determine individually-specific methods for improving adherence (Zygmunt, Olfson et al. 2002). Weiden (2007) proposes a flexible approach to applying adherence theory in individuals taking antipsychotics that may lead to an enhanced range of potential therapeutic interventions to limit the effects of non-adherence. This approach distinguishes adherence attitudes from adherence behaviour and points out that each needs to be assessed and managed to improve medication taking behaviour.

In addition to the valuable information that can be gained in future from qualitative research, how best to incorporate the impact of non-adherence in quantitative analysis needs to be addressed. One issue is how best to standardise the measurement and reporting of adherence. Cramer et al (2008) propose that adherence should be reported in studies as the percentage of dosages missed in a particular period of time. This continuous measure would reflect the severity of non-adherence and would avoid situations where different cut-points indicating non-adherence are used across studies. They suggest that in prospective studies, the percentage of dosages missed would be available from electronic monitoring and in retrospective studies the medication possession ratio would provide the necessary information to allow for this index to be calculated. Electronic monitoring and the medicine possession ratio methods, however, are not without limitations and are unlikely to be feasible in large surveys. Hughes et al (2001) have recommended using a measure of non-adherence, such as the therapeutic coverage achieved and relating it to changes in outcome at different levels of exposure over time. This would take into account the timing of missed dosages, which may be important to the effectiveness of the medication.

Another important question is how best can cost-effectiveness analysis (CEA) take account of longer term outcomes which will reflect the true impact of non-adherence to medication? In a review of literature evaluating both costs and clinical outcomes in schizophrenia, none of the trials used for CEA evaluated costs and effects beyond the first year of treatment (Basu 2004). The fact that these trials were funded by pharmaceutical companies and employed methods that would meet marketing regulatory requirements only meant that it would be impractical

for them to take a long-term perspective, in part due to the costs involved. Long-term studies incur substantial costs in following patients and in data collection. Moreover, studies involving schizophrenia patients have very high sample attrition (Verhoeven, Van der Heijden et al. 2005; Vickar, North et al. 2009). These costs may be warranted, however, given that short-term studies do not address effects and costs that appear in the longer term, when the impacts of non-adherence may realised, especially in a chronic illness such as schizophrenia.

Historically, analyses of randomised control trials to assess clinical effectiveness have adopted intention-to-treat analysis when participants do not receive the intervention or course of treatment to which they were randomised. Thus those individuals who do not adhere to their treatment would contribute outcome data towards the group to which they were assigned. This approach requires two important assumptions to be made (White 2005). Firstly, that the benefit of treatment is the same for all individuals, regardless of whether they are more or less likely to adhere to their medication. Secondly, that the difference in costs between the treatment and control group depends only on the difference in intervention costs. The latter assumption can not be made in drug trials where there are cost implications of non-adherence. Cost-effectiveness evaluations of drug therapies should include sensitivity analysis to determine if realistic rates of non-adherence have a bearing on the outcome of the evaluation (Hughes, Bagust et al. 2001). Note that while the focus here is not on the clinical consequences on non-adherence, these too are important.

Table 6.1 is a subset of part of Table II in Hughes et al (2001). The original table attempts to categorise drug-disease pairs according to the sensitivity of their cost-effectiveness ratios to changes in adherence taking into account the nature of the disease and the severity of the consequences of non-adherence. The table estimates these impacts for a range of illnesses including psychosis and depression. The economic consequences are represented as £ (least costly), ££ or £££ (most costly) which are hypothesised costs per quality-adjusted life-year (QALY) per percentage decrease in drug regimen non-adherence or premature treatment discontinuation. These, however, are only estimates. Information on the frequency of missed dosages would be necessary to determine the effects on the pharmacodynamic interaction of a drug with the disease process it was prescribed for. This is partly reflected in the perceived impact of non-adherence relative to premature discontinuation of medication for a potentially fatal disease such as hypertension.

Table 6.1: Examples of the clinical consequence of noncompliance estimated according to hypothesised costs per quality-adjusted life-year per percentage decrease in drug regimen

Disease	Drug treatment	Drug regimen noncompliance		Premature discontinuation	
		Clinical consequences	£/QALY/%	Clinical consequences	£/QALY/%
Psychosis	Antipsychotics	Extended duration of symptoms	££	Increased risk of suicide	££
Depression	Antidepressants	Relapse of depression	££	Discontinuation syndrome	££
Osteoporosis	Bisphosphonates	Decreased bone density	£	Increased risk of fractures	££
Hypertension	Diuretics	Increased blood pressure	£	Increased risk of cardiovascular events	£££
Heart failure	Diuretics	Acute fluid retention	£££	Increased risk of cardiovascular events	£££

Source: Hughes et al 2001b

A variety of modelling techniques have been employed in the recent literature to deal with the methodological difficulties in observing the long-term economic consequences of non-adherence. The three main techniques used are decision-analysis or decision trees, Markov models and Discrete Event Simulation (DES). In decision-analysis models there is a 'root' decision from which branches extend, representing different events or secondary decisions. Each branch has associated with it a probability of the event it relates to occurring. To reflect non-adherence, levels of adherence can be branches within a decision tree, each assigned a probability. Cost and effect consequences of each branch are typically represented at the end point of each sequence of branches. The weighted average of outcomes can then be calculated to arrive at the average effect and/or cost of each branch of the decision tree. Decision-analysis models usually attempt to model a limited number of outcomes for the average patient. Attempting to incorporate variability across patients would require analysing the model with different event probabilities or building separate branches for different subgroups (Heeg, Damen et al. 2008). Similarly, decision-analysis models are also constrained by not

modelling variability in patient characteristics over time. To incorporate variability over time, the model would require branches for each time period, exponentially increasing the number of branches.

A Markov model is a repeated decision tree in which events are modelled as transitions from one health state to another over time (Heeg, Damen et al. 2008). As in decision-analysis, Markov models become very complex when made to account for subgroups of patients. This method of modelling is also constrained by the assumption that the probability of an event is not affected by previous occurrences of the event. This assumption does not hold in schizophrenia where the risk of relapse or non-adherence is not independent of previously experienced relapses, so micro-simulation Markov models have been developed to simulate individual patient histories over time (Heeg, Damen et al. 2008).

Discrete Event Simulation Models represent the dynamic behaviour of a system. They are able to represent multiple factors in a model simultaneously (Heeg, Buskens et al. 2005). Time-independent parameters, such as sex, can be assigned a probability distribution and time-dependent variables, such as adherence or non-adherence, are simulated as part of patient histories. This feature of DES models allows them to assess outcomes over longer-term time horizons. Data for a large number of individuals can be run through the model to arrive at aggregate clinical outcomes and costs.

Each of the modelling approaches require data from the literature or expert opinion as to the probability of events such as non-adherence and the clinical and cost consequences of these events. Typically, sensitivity analyses are run to determine the impact of varying the probability of non-adherence. The results produced in this thesis could be used to contribute estimates of the cost consequences on non-adherence to such model.

Hughes et al (2007) conducted a review of pharmacoeconomic evaluations published between 1997 and 2005 that included non-adherence in the evaluation process and found no consistency in the modelling techniques used. The authors note that Health Technology Assessment bodies have not published consensus guidelines on the use of these techniques.

6.4 Conclusions

The impact of non-adherence on health, social care and the wider societal costs is difficult to assess for practical and methodological reasons. Analyses of nationally representative samples of individuals prescribed antipsychotics and antidepressants suggest that younger age, illness severity and the experience of side-effects are common causes of non-adherence in mental illness. Substance abuse is an additional factor associated with non-adherence in patients taking antipsychotics.

Community-based services were found to be used more by individuals with interruptions in their antipsychotic medication. In this group there may also be additional costs in hospitalisations and overall health and social care services attributable to non-adherence. Benefits to patients may be accrued by enabling health and social care professionals, particularly those working in the community, to encourage medication adherence in individuals with schizophrenia and to provide information on new interventions that are cost-effective in improving adherence.

The datasets used in my analyses were the best available sources of data at the time of my analyses. Further analysis in this area is warranted. At the level of the individual, qualitative research methods may contribute to our understanding of the reasons why some people with schizophrenia choose not to take their medication. More long-term studies are needed to determine the clinical, economic and personal consequences of non-adherence. Greater standardisaton of the way in which non-adherence is assessed in these studies would be beneficial. The data provided from these studies will be particularly useful in assessments of the long-term cost-effectiveness of new medicines and therapies to treat schizophrenia.

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APPENDIX

APPENDIX 1: Results of literature search for empirical studies looking at factors associated with non-adherence in schizophrenia

APPENDIX 2: Patterns of, and factors associated with, atypical and typical antipsychotic prescribing by general practitioners in the UK during the 1990s

APPENDIX 1

Results of literature search for empirical studies looking at factors associated with non-adherence in schizophrenia

Author, date	Country	Sample size	Sample	Adherence assessment	Study time period	Factors associated with non-adherence	Factors not associated with non-adherence
Swartz et al, 2001	US	258	Outpatients with psychosis	Self-reported, family, case-manager	1 year	Involuntary outpatient commitment, African-American ethnicity, substance abuse, low GAF score	Age, urban v rural, sex, marital status, income, education, social support, homelessness, victim of crime, Brief Symptom Inventory score, insight into illness, prior psychotic hospitalisation
Trauer et al, 2000	Australia	218	Outpatients with psychosis	Self-report, physician, case-manager	1 month		Insight into illness
Weiss et al, 2002	US	162	Ambulatory with psychosis	Therapist	Time to non-adh. or end of study	Low GAF score, substance abuse, poor working alliance with therapist	Demographic factors, illness history
Ruscher et al, 1997	Canada	148	Inpatients and outpatients with psychosis	Self-report	6 months	High educational attainment, currently an inpatient	Class of antipsychotic, sex, age, marital status, diagnosis, number of previous admissions, length of hospitalisation
Rittmannsberger et al, 2004	Austria	95	Outpatients with psychosis	Self-report	1 month	Low GAF score, irregular contact with treating psychiatrist, increased age	

GAF – Global Assessment of Functioning (measures social, psychological and occupational functioning

Author, date	Country	Sample size	Sample	Adherence assessment	Study time period	Factors associated with non-adherence	Factors not associated with non-adherence
Grunebaum et al, 2001	US	74	Residents of supported housing with psychosis	Self-report	1 month	Lack of medical supervision, negative view of psychiatric medicines, low GAF score	Class of antipsychotic, medication regime complexity
Kampman, 2002	Finland	59	Inpatient and outpatient with first-onset psychosis	Self-report	3 months	Side effects, male, lack of social acitivities, low PANSS positive symptoms subscale score, high PANSS total score, younger age	
Ziguras et al, 2001	Australia	168	Outpatients with psychosis	Case-managers' report		Poor cooperation with staff, poor insight, problems with impulse control, less ability to manage finances, case-manager from different ethnic background	Age, sex, receipt of depot medication, size of social network, drug or alcohol abuse, medication dose, thought disorder
Coldham et al, 2002	Canada	200	Outpatients with first-episode psychosis	Medical records (reviewed by study first author)	1 year	Positive symptoms, substance abuse, low insight, younger age, younger age at onset of illness, lack of family support	
Hudson et al, 2004	US	153	Inpatients and outpatients with schizophrenia	Self-report and medical records	30 days	Lower level of education, substance abuse, high PANSS total score, barriers to taking medication (e.g. stigma), adverse drug reactions, forgetfulness, lack of social support	Age, sex, marital status, ethnicity, premorbid functioning, SF-36 score, Barnes Akathisia Scale score
Owen et al, 1996	US	135	Inpatients with schizophrenia	Self-report with input from family and health professionals	30 days	Substance abuse	Living arrangements

PANSS – Positive and Negative Syndrome Scale (measures schizophrenia symptom severity)
SF-36 – Short Form 36 (measures health state)

Author, date	Country	Sample size	Sample	Adherence assessment	Study time period	Factors associated with non-adherence	Factors not associated with non-adherence
Holzinger et al, 2002	Germany	77	Inpatients or day hospital patients with schizophrenia	Self-report, family	1 month	Quality of helping alliance, delusion of grandiosity, attitude towards antipsychotic drugs	Perceptions of mental illness and prognosis
Rettenbacher et al, 2004	Austria	61	Schizophrenia outpatients with recent inpatient stay	Self-report and plasma levels of antipsychotic	3 months	Positive effect of drugs on illness, psychiatrist's inquery into drug taking, psychological side effects	PANSS subscales
Weiden et al, 2004	US	239	Outpatients with schizophrenia	Self-report	Week of missed medication (if ever missed)	obesity	Sex, class of antipsychotic, satisfaction with psychiatrist, length of time on medication, general well-being, attitude to medication
Valenstein et al, 2004	US	63,214	Inpatients and outpatients with schizophrenia	Medication possession ratio	1 year	African-American ethnicity, younger age, low dose	Class of antipsychotic
Robinson et al, 2002	US	112	Inpatients and outpatients with schizophrenia	Self-report, family, health professionals	1 year	Poor premorbid cognitive ability	Demographics characteristics, premorbid social functioning, time to start of treatment, diagnosis, illness severity, presence of motor side effects, family attitudes
Hunt et al, 2002	Australia	99	Schizophrenia patients requiring acute or crisis care	Medical records	4 years	Substance abuse	

PANSS – Positive and Negative Syndrome Scale (measures schizophrenia symptom severity)

Author, date	Country	Sample size	Sample	Adherence assessment	Study time period	Factors associated with non-adherence	Factors not associated with non-adherence
Kamali et al, 2001	Ireland	87	Inpatients with schizophrenia suffering acute relapse	Self-report, family, mental health professionals	1 month	Substance abuse, negative subjective response to medication, lack of insight	Age, sex duration of illness, dosage of medication
Novak-Grubic et al, 2002	Slovenia	56	Outpatients with schizophrenia after first episode	Self-report, family	1 year	Poor insight, positive symptoms at admission, diagnosis	Socio-demographics characteristics, severity of extra-pyramidal symptoms, class of antipsychotic, attitude towards hospitalisation, length of hospital stay
Diaz et al, 2004	US	50	Individuals with schizophrenia in a community mental health centre	Medication Event Monitoring System	3 months	Male, dose frequency	Class of antipsychotic, Barnes Akathisia Scale
Liraud et al, 2001	France	45	Inpatients with schizophrenia	Self-report, medical records	1 year	Sensation-seeking	Impulsivity, experience-seeking
Donohue et al, 2001	Ireland	32	Inpatients with schizophrenia	Clinical rating following interview	3 months	Attitude to medication, PANSS activation and composite subscales, poor memory	Age, sex, time since diagnosis, level of education, living arrangements, schizophrenia subtype, substance abuse
Lambert et al, 2004	Germany	213	Inpatients with schizophrenia prescribed first-generation ('typicals') antipsychotics	Self-report, medical records	1 month	Negative attitude towards antipsychotics, side effects	Age, sex, level of education, age at onset of illness, length of illness, medication dosage, number of prior admissions, psychopathology, duration of untreated psychosis

PANSS – Positive and Negative Syndrome Scale (measures schizophrenia symptom severity)

Author, date	Country	Sample size	Sample	Adherence assessment	Study time period	Factors associated with non-adherence	Factors not associated with non-adherence
Olfson et al, 2000	US	213	Outpatients with schizophrenia within 3 months of an inpatient stay	Self-report	3 months	Substance abuse, prior non-adherence, family refusal to participate in treatment, poor involvement in treatment	class of antipsychotic, symptom severity
Becker et al, 2007	US	10,330	Outpatients with schizophrenia	Frequency of refills	2 years	Younger age, female, Non-White ethnicity, prescribed first-generation ('typical') antipsychotic, substance abuse	
Asher-Svanum et al, 2006	US	1,579	Inpatients and outpatients with schizophrenia	Self-report and medical records	3 years	Prior non-adherence, drug and alcohol abuse, prior treatment with antidepressants, medication-related cognitive impairment	
Valenstein et al, 2006	US	33,760	Inpatients and outpatients with schizophrenia	Medication possession ratio	4 years	Younger age, African-American or Hispanic ethnicity, substance abuse, psychiatric hospitalisation, low dosage of medication, prescribed first-generation ('typical') antipsychotic	Sex
Yen et al, 2005	Taiwan	74	Outpatients with schizophrenia	Medication Adherence Behaviour Scale score based on patient interview, family	1 year	Religious belief, non-adherence at baseline	Sex, marital status, occupation

PANSS – Positive and Negative Syndrome Scale (measures schizophrenia symptom severity)

Author, date	Country	Sample size	Sample	Adherence assessment	Study time period	Factors associated with non-adherence	Factors not associated with non-adherence
McCann et al, 2008	Australia	81	Outpatients with schizophrenia	Factors Influencing Neuroleptic Medication Taking Scale based on patient interview		Younger age, side effects, poor access to psychiatrists	Living arrangements, level of insight, stigma experienced, alcohol abuse, social support, access to case-manager and GP
Cooper et al, 2007	Canada	4,495	Outpatients with schizophrenia	Medical records	1 year	Low intensity treatment, initiated on olanzapnie, prescribed first generation ('typical') antipsychotics, low comorbidity index, substance abuse, younger age, not on welfare or income support	
Karow et al, 2007	Germany	2,414	Inpatients and outpatients with schizophrenia	Self-report , physician	1 year	Severity of positive symptoms, lack of improvement in positive symptoms	Negative, depressive and cognitive symptoms, improvement in negative, depressive and cognitive symptoms, improvement in side effects
de Haan et al, 2007	The Netherlands	119	Inpatients and outpatients with schizophrenia	Self-report, health professionals	5 years	Hostility and uncooperativeness, involuntary admission	Subjective well-being, ROMI scale score, insight, PANSS score
Perkins et al, 2008	US and Canada	234	Inpatients and outpatients with schizophrenia (first episode)	Self-report, physician	1 year	Substance abuse, comorbid depression, Black ethnicity, higher cognitive performance	Duration of illness, side effects

PANSS – Positive and Negative Syndrome Scale (measures schizophrenia symptom severity)
ROMI – Rating of Medication Influences Scale (measures reasons patients give for taking or not taking their medication)

Author, date	Country	Sample size	Sample	Adherence assessment	Study time period	Factors associated with non-adherence	Factors not associated with non-adherence
Klingberg et al, 2008	Germany	108	Inpatients and outpatients with schizophrenia	Physician	1 year	Lack of trust in medication, lack of insight	Problem solving ability, socio-demographic factors, comorbidity, age at onset of illness, PANSS score, class of antipsychotic, number or severity of side effects, social contact
Kamali et al, 2006	Ireland	100	Inpatient with psychosis (first episode)	Self-report	6 months	Positive symptom score, drug and alcohol abuse, lack of insight	Age, sex, negative symptom score, voluntary versus involuntary admission
Janssen et al, 2006	Germany	670	Inpatients with psychosis	Self-report, health professionals	Length of admission	Substance abuse, history of aggressive behaviour, involuntary admission, lower level of education, PANSS negative symptom score, PANSS paranoid/belligerence score	Household composition, employment status, side effects, class of antipsychotic
Ramirex Garcia et al, 2006	US	30	Outpatients with schizophrenia	Patient records, physician, family	9 months	Instrumental support from family	Emotional support, criticism, emotional under-involvement
Perkins et al, 2006	US	254	Inpatients and outpatients with schizophrenia	Pill counts	2 years	Low belief in need for treatment, low belief in benefit of medication, clinically-rated akathisia no weight gain, inpatient, low improvement in positive symptoms	Age, negative aspects of medication, social support, duration of illness, ethnicity, neurocognitive function, PANSS score improvement, marijuana use

PANSS – Positive and Negative Syndrome Scale (measures schizophrenia symptom severity)
ROMI – Rating of Medication Influences Scale (measures reasons patients give for taking or not taking their medication)

Author, date	Country	Sample size	Sample	Adherence assessment	Study time period	Factors associated with non-adherence	Factors not associated with non-adherence
Lecomte et al, 2008	Canada	147	Outpatients with schizophrenia	Self-report	Cross-sectional	Positive symptoms, witnessed violence as a child, agreeableness	Neurosis, negative symptoms, insight, drug and alcohol abuse
Heinrichs et al 2008	Canada	147	Outpatient with schizophrenia	Medical Management Ability Assessment	Cross-sectional	Cognitive function	
Mutsatsa et al, 2003	UK	101	Inpatients and outpatients with schizophrenia	Health professionals	12 weeks	Insight, negative attitude towards medication	Drug and alcohol abuse, side effects, severity of illness
Jeste et al, 2003	US	110	Outpatients with schizophrenia	Medical Management Ability Assessment	Cross-sectional	Cognitive function	Age, sex, level of education, living arrangements, symptom severity, attitude towards medication

PANSS – Positive and Negative Syndrome Scale (measures schizophrenia symptom severity)

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APPENDIX 2

Patterns of, and factors associated with, atypical and typical antipsychotic prescribing by general practitioners in the UK during the 1990s

Introduction

The development of atypical (or second generation) antipsychotics has offered people with schizophrenia a potentially more effective and less damaging set of treatment options. Atypical antipsychotics are more expensive than the earlier class of antipsychotics (which are no longer patented), but are argued to be more effective in alleviating symptoms of the illness and to be associated with fewer side-effects (Leucht et al. 1999; Sartorius et al. 2002; Sartorius et al. 2003). By reducing side-effects, for example, atypical antipsychotics may reduce non-adherence to medication, which significantly increases the probability of relapse into an acute schizophrenic episode (Weiden and Olfson 1995), and in turn pushes up treatment and support costs (Almond et al. 2004). Thus, support for prescribing of atypical antipsychotics, relative to typical antipsychotics, in treating patients with schizophrenia, has also been made on cost-effectiveness grounds (Davis et al. 2003; Hudson et al. 2003), although the evidence is not unequivocal (Basu 2004; Duggan 2005).

Data from IMS indicate that sales of antipsychotics in the United Kingdom increased ten-fold between 1996 and 2002, a trend matched in a number of other European countries (IMS Health 2003). The introduction and uptake of atypical antispychotics has been the primary reason. A number of local studies of prescribing patterns in primary care in the UK show rapid increases in the use of atypical antipsychotics. For example, between 1994 and 1997, a 28% growth in prescriptions in Scotland was observed (Stark et al. 2000); between 1996/7 and 2000/1, there was a six-fold increase in the volume of atypical antipsychotics prescribed in the West Midlands (Ashcroft et al. 2002); and for a similar period there was a twenty-fold rise in expenditure on atypicals in Greater Manchester (Hayhurst et al. 2003). In July 2002, the National Institute for Clinical Excellence (NICE) published guidance favouring the use of atypical antipsychotics as a first line treatment for patients with schizophrenia (NICE 2002), which may be expected to further boost growth (Walley 2004).

Overall, the percentage of mental health drugs prescribed by general practitioners in England accounted for by antipsychotics has increased only slightly since 1998 to about 10%. However, they represent more than 21% of spending on mental health drugs in primary care, a proportion that has grown from approximately 12% in 1998 (source: Prescribing analysis and cross tabulation data). The rise in spending is entirely due to switching from low price typical antipsychotics to the more expensive atypical antipsychotics (despite inflation-adjusted prices for the latter having dropped over time).

Using national data on primary care prescribing, Kaye et al (2003) calculated that antipsychotic use increased from 10.5 people per 1000 population in 1991 to 12.2 per 1000 in 2000, with most of the increase – and indeed most of the use – to treat non-prescribing of atypical antipsychotics in the treatment of schizophrenia. My analysis, like that by Kaye et al, is based on the General Practice Research Database (GPRD). Importantly, the GPRD allows us to follow people with schizophrenia and schizoaffective disorder over a number of years in order to assess changes in the prescription of atypical antipsychotics over time and – a particular focus of my work – to explore some of the individual characteristics associated with these changes.

Methods

General Practice Research Database

The GPRD is a computerised database of anonymised general practice patient records that commenced in 1987 and now contains over 30 million patient years of information. Currently, the database collects information on approximately 3 million patients: approximately 4.7% of the UK population. Data are provided by a cross-section of practices, across the UK. Information is recorded by GPs on demographics, medical diagnosis, all prescriptions, referrals to hospitals, hospital discharge reports where patients are referred to hospital for treatment, and treatment outcomes (crudely measured) (Wood and Coulson 2001). The GPRD is used for academic and policy-related research, and also by the United Kingdom Medicines and Healthcare products Regulatory Agency, primarily for better understanding of drug safety issues brought to its attention by GPs submitting adverse drug reaction reports. The quality and completeness of

these data for research have been confirmed by several validation studies (Walley and Mantgani 1997).

As atypical antipsychotic medications were not prescribed in the UK before 1993, my study used data from 1st January 1993 through to 31st December 1999. A legal dispute between the data owners and the data vendors resulted in the rapid decline in the number of patients available in the database. For this reason, data for 2000 and 2001 are excluded. I did not look at later (post-2001) data because I chose to employ a panel design based on linking annual GPRD datasets from one year to the next.

Schizophrenia and schizoaffective patients

My inclusion criteria required a patient to have received at least one prescription for an antipsychotic medication, be enrolled in the General Practice Research Database for the entire year and have been diagnosed with schizophrenia or schizoaffective disorder prior to the beginning of that year. There were no other inclusion or exclusion criteria.

Read codes (now simply called the Clinical Terms in the UK) provide the diagnostic classification used to identify patients with schizophrenia or schizoaffective disorder. The Read codes were introduced in the UK in 1986 to generate computer summaries of patient care in primary care. In the subsequent revision (Version 2), their structure was changed and based upon the International Classification of Diseases (ICD)-9 and OPCS-4, the Classification of Surgical Operations and Procedures. Schizophrenia disorders are identified by Read codes E100-106, E10y, E10z or Eu20; schizoaffective disorder by Read codes E107 or Eu25.

My identification of users of antipsychotic drugs was similar to the method employed by Kaye et al (2003). They too identified patients who had at least one prescription for an antipsychotic during the year. There are, however, important differences. They did not limit their analysis to schizophrenia and schizoaffective patients, and only used data from 270 general practices that had an uninterrupted record of data contribution to the GPRD.

Antipsychotic drugs

Medications are the most reliably recorded resource category in the GPRD given the separate and detailed prescription records in the database. The drug name (generic and method of administration), daily dose (mg, ml, etc.) and duration of therapy (days) of all prescriptions made by the GP are recorded in the database. The atypical antipsychotic medications observed in the dataset are: amisulpride, clozapine, olanzapine, quetiapine, remoxipride, risperidone, sertindole, and zotepine. These drugs were not all marketed for the full period under study here. The date of licensing for each of the drugs appears in Table 1. For comparison, Kaye et al (2003) identified patients who received a medication listed as an antipsychotic on the British National Formulary, but excluded from their analysis the use of clozapine, benperidol, sertindole, amisulipride and quetiapine on the basis that each of these drugs were prescribed to fewer than 1,000 patients during the study period.

Linking of annual datasets

I linked patients over time to allow panel analyses to be conducted (see below). Data for each year from 1993 to 1999 were sorted, and then merged on the unique patient number. This means that the number of observations per patient will vary, depending upon the number of years in which they met the inclusion criteria.

Statistical analysis

By linking annual datasets I created a longitudinal (also called panel) dataset which then allowed me to analyse changes over time. Longitudinal data designs of this kind are very helpful because they allow for separate estimation of the effects of differences between subjects, and of time-series or within-subject effects reflected in the changes within subjects over time. Panel data regression techniques allow one to take advantage of these different types of information. A panel logistic regression model was run in STATA (2001). A model was fitted to the data to determine factors influencing the choice between typical and atypical antipsychotics, with the dependent variable as positive if the patient received an atypical antipsychotic and negative if they did not.

Table 1: Licensing period of atypical antipsychotic medications observed in the GPRD dataset

Drug name	*Year licensed*	*If withdrawn, Year*	Comments
Amisulpride	1997		
Clozapine	1995		
Olanzapine	1996		
Quetiapine	1997		
Remoxipride	1986	1993	Withdrawn due to reports of aplastic anaemia[1]
Risperidone	1993		
Sertindole	1996	1998	Withdrawn due to concerns about effects on the heart; Reinstated with restricted license in 2002 requiring strict monitoring and guidelines of use[2]
Zotepine	1998		

[1] Northern and Yorkshire Regional Drug and Therapeutics Centre. 'The Use of Atypical Antipsychotics in the Management of Schizophrenia' February 1998. Accessed on-line on 23 January 2006 at: http://www.nyrdtc.nhs.uk/docs/eva/atypical_antipsychotics.pdf

[2] Norfolk and Waveney Mental Health Partnership NHS Trust Pharmacy Medicine Information. Accessed on-line on 23 January 2006 at: http://www.nmhct.nhs.uk/pharmacy/dsertind.htm

A random-effects model was employed because I assumed that while some omitted effects may be constant over time but vary between cases (e.g. the confidence of the patient in expressing a preference for atypical antipsychotics), others may be fixed between cases but vary over time (e.g. the relative price of atypicals to typical antipsychotics). Also, the STATA output includes a significance test of the proportion of the total variance in the data contributed by the panel-level variance component. If this test returns a finding of significance, this justifies the panel specification of the model which accounts for both the variability within patients over time, and the variability between patients. Significance levels at the 0.05 level or below were deemed statistically significant.

Results

Of patients with schizophrenia or schizoaffective disorder who contributed data in 1999, 20.8% were prescribed an atypical antipsychotic during that year. At the start of the study period, atypical antipsychotic prescribing was much lower: 1.8% in 1993. Full data on the rate of atypical prescribing in each year of the study period appear in Table 2. At the beginning of this period, the most widely prescribed atypical antipsychotic was remoxipride (IMS Health 2003b), but this drug was withdrawn in 1994 due to reports of aplastic anaemia (Northern and Yorkshire Regional Drug and Therapeutics Centre 1998). From 1994 to 1997, the atypical antipsychotic with the largest market share was risperidone, but in 1998 and 1999 it was overtaken by olanzapine as the most widely used atypical antipsychotic (IMS Health 2003b).

A panel logistic regression model (random effects) was run on 4,391 patients in the database for 1993 to 1999 who had a diagnosis of schizophrenia or schizoaffective disorder and received at least one antipsychotic medication prescription in each year that they contributed data to my sample. Statistically significant associations were observed between choice of antipsychotic medication and three variables: age, having an inpatient stay in the previous year and having six or more primary care visits in the previous year (see Table 3). Older patients were less likely to be prescribed an atypical as compared to a typical antipsychotic. For every five-year difference in age the probability of being prescribed an atypical antipsychotic decreased by 15%. Patients who had an inpatient stay in the previous year were over 1.5 times as likely to receive atypical antipsychotics, as were patients who had visited their GP six or more times in the previous year. Gender and time since first diagnosis of

Table 2: Rate of atypical prescribing in general practice for patients with schizophrenia or schizoaffective disorder: 1993-1999

Year	Atypical antipsychotic prescribing among GPRD schizophrenia and schizoaffective patients prescribed antipsychotics	
	N	%
1993	69	1.8
1994	102	2.7
1995	129	3.7
1996	166	5.7
1997	232	9.2
1998	277	13.8
1999	228	20.8

Source: General Practice Research Database.

Table 3: Panel logistic regression on GRPD data (1993-1999) looking at factors associated with receipt of atypical antipsychotics

N = 4,391
Average number of observations per subject = 3.3

Wald chi-squared statistic = 78.71
Prob > chi2 = 0.0000

	Coefficient	Odds ratio	p-value
Age – 5 year increase	**-0.1640**	**0.85**	**<0.001**
Sex – Male relative to female	0.2609	1.30	0.121
Time since diagnosis of schizophrenia – 5 year increase	0.0285	1.03	0.557
Inpatient in the previous year	**0.5206**	**1.68**	**<0.001**
6 or more GP visits	**0.5165**	**1.68**	**<0.001**
Constant	**-4.3596**		
Panel-level variance component (log of the standard deviation)	2.2674	0.1066	
Standard deviation	3.1072	0.1656	
Proportion of total variance contributed by the panel-level component	0.7458	0.0202	

Liklihood ration test of rho=0: chibar2(01) = 1258.70 Prob >= chibar2 = 0.000

Note: random effects model with subject effect included.

schizophrenia or schizoaffective disorder were not associated with higher or lower odds of being prescribed an atypical antipsychotic.

A test of the contribution to the model of having repeated observations from each patient suggests that the design of the model, which accounts for the fact that there is variability within patients over time and between patients, is justified.

Discussion

Trends in the rate of prescribing of atypical antipsychotics

Within my primary care study sample, a tenfold increase in the rate of atypical antipsychotic prescribing was observed between 1993 and 1999. This rate of growth is comparable to UK data from other sources, although none appear to have looked at as wide a sample as I was able to examine in this paper. For example, a six-fold increase in retail sales of atypical antipsychotics was observed in IMS Health data for the period 1996 to 1999 (IMS Health 2003).

Local studies of prescribing have also found comparable growth rates, and have the advantage of looking at a more recent period. In the West Midlands between 1996/7 and 2000/1 there was a six-fold increase in the volume of atypical antipsychotics prescribed. The authors calculated defined daily dose at the health authority level by adjusting for differences in population size and age stratification (Ashcroft et al. 2002).

Hayhurst et al (2003) observed greater increases in Greater Manchester over the same period (1996/7 to 2000/1), but these increases varied markedly across health authorities. For a three-month period in 1999, the adjusted per capita expenditure on atypical antipsychotics ranged from less than £75 to over £500 and the variation between health authorities in per capita expenditure on atypical drugs was almost three times greater than the variation in per capita expenditure on typical antipsychotics.

With regards to prescribing patterns subsequent to the data used in this study, data from the NHS Prescription Pricing Authority indicate that the rate of atypical antipsychotic prescribing

in General Practice in England has increased from 21.3% in June 2000 to 61.1% in June 2005 (NHS Prescription Pricing Authority 2006). These data are not comparable to the GPRD data, however, as they include prescribing for indications other than schizophrenia and schizoaffective disorder and relate to rates in England only, as compared to the GPRD which incorporates data for all of the UK.

Factors associated with atypical antipsychotics prescribing

My analysis has been able to identify some significant correlates of prescription choice, notably age, previous inpatient stay and previous frequency of primary care consultation.

Age

The NICE guidelines issued in 2002 did not suggest that age should be taken into account in the prescription choice. The NICE guidelines do recommend that patients whose illness is stable on typical antipsychotics should not be switched to atypical antipsychotics. It is possible that older patients, having had their illness for a longer period of time (the age of onset of schizophrenia being almost always in early adulthood), are more likely to have been stabilised on a typical antipsychotic. My model tests for the effect of age separately from time since diagnosis, but this effect was not found to be statistically significant. One conclusion would thus be that other interpretations of the age effect are warranted. It is the case, however, that age and time since diagnosis are significantly correlated ($r=0.49$ in 1999; $p<0.0001$), so some degree of collinearity cannot be ruled out.

It may be the case that more of the younger patients in the sample are newly diagnosed and are more likely to be receiving an initial prescription for atypical antipsychotics. For these patients, the NICE guidelines – which obviously postdate the period studied in this paper – suggest that atypical antipsychotics should be considered. Alternatively, this result may be due to GPs being more defensive in their prescribing to older patients. There have been concerns that atypical antipsychotics increase the risk of ischaemic stroke in patients with dementia (Wooltorton 2002), and while these concerns were not extended to patients with schizophrenia, it may be the case that clinical experience ahead of the formal issue of such

warnings affected the prescription choice for GPs prescribing for older patients (Percudani et al. 2005). Recent studies have subsequently found no statistically significant increased risk of ischaemic stroke for dementia patients taking atypical antipsychotics as compared to typical antipsychotics (Gill et al. 2005).

There is also evidence that discrimination may affect the prescribing choice. Studies in the US have concluded that ethnic minority patients are less likely to be prescribed atypical antipsychotics relative to the general population (Valenti et al. 2003; Opolka et al. 2004). It may be the case that similar discrimination occurs against older schizophrenia and schizoaffective disorder patients.

Inpatient stays in the previous 12 months

The GPRD data indicate that over time, patients with recent inpatient stays were more likely to be prescribed atypical antipsychotics. If it is reasonable to assume that inpatient admission follows an exacerbation of symptoms, then it can be inferred from this result that, in line with the NICE guidance, patients with more severe illness, or whose illness has not been stabilised, are more likely to be prescribed atypical antipsychotics. Alternatively, this result may reflect a preference of prescribing atypical antipsychotics, for acute patients, by hospital-based psychiatrists. The prescription choice would then be continued by the patient's GP once they were discharged from hospital.

A US study by Duggan (2005), on individual patient Medicaid data, found a significant increase in the use of inpatient care in the days leading up to an initial prescription for an atypical antipsychotic. This suggests that patients were started on atypical antipsychotics as a consequence of their previous medication not preventing an acute episode. Therefore, this result is not likely to be due to comorbidity, but instead the result of the severity of symptoms present in an acute hospital setting.

GP visits in the previous 12 months

Evidence supporting the significance of comorbidity in the prescription choice can be found in my result that there is an increased likelihood of atypical prescribing among patients with

several recent visits to their GP. For some patients this may be for side-effects experienced as a result of their antipsychotic medication.

The setting of care may also be a key factor in the prescription choice. Just as hospital psychiatrists may prescribe more atypical antipsychotics as they are often treating acutely ill patients, the prescribing of antipsychotics in primary care may be affected by a GP's experiences. Mortimer (2003) suggests that where antipsychotics are prescribed in primary care, there may be a preference for using the older typical antipsychotics as GPs are more likely to be familiar with these drugs. As the GPRD data are primary care-based, there may be a bias in lower rates of atypical antipsychotic prescribing in these data.

Significant findings from other studies

Taylor et al (2000), in their study of inpatient prescribing, found an association between gender and the use of atypical antipsychotics. They found that men were more likely to receive atypical antipsychotics. This result was not substantiated by my analysis: I found no significant gender difference.

In reaching treatment decisions, physicians are to some extent influenced by the extent of their postgraduate education, the views of local colleagues, staff shortages (encouraging, it has been argued, wider use of depot medications), pharmaceutical company advertising, the requests of patients and budgetary constraints (Hogman 1996; Bebbington 2001; Hayhurst et al. 2003; Walley 2004). For example, despite recommendations against either practice, there is evidence that for patients with severe symptoms, psychiatrists often prescribe excessive dosages or prescribe more than one antipsychotic (Taylor et al. 2000; Mortimer 2003; Paton et al. 2003). Further, there is evidence that in primary care, familiarity with the content of the National Service Frameworks in mental health is poor (Rogers et al. 2002).

Limitations

This study is potentially limited by the scope and content of the source of data. The GPRD includes prescribing data at the outpatient level only. This includes prescribing initiated by the

GP or by a specialist in an outpatient setting. The dataset does not include records of hospital inpatient prescribing, which may represent a sizeable proportion of antipsychotic prescribing. Data from IMS Health on sales of atypical antipsychotics in the United Kingdom indicate that in 2002 approximately 33% of prescriptions for atypical antipsychotics were made within hospitals (IMS Health 2003).

The analysis of factors impacting on medication choice is limited by the lack of more detailed data on the characteristics of patients, and medical practitioners, included in the sample. It has been suggested by other UK studies that receipt of an atypical rather than a typical antipsychotic is linked to factors such as treatment history and risk of non-adherence (Hogman 1996; Mortimer 2003).

Conclusions

The trend of an increase in the rate of atypical antipsychotic prescribing in schizophrenia, as a percentage of all antipsychotic prescribing, is likely to continue, unless clear evidence is forthcoming that the side-effects attributable to atypical antipsychotics are more debilitating than those associated with typical antipsychotics (Bushe and Leonard 2004). Reductions in their real prices, relative to typical antipsychotics, seems likely to encourage GPs to prescribe atypical antipsychotics more frequently in preference to the older medications. What is not clear is if the rate of increase will be above what was observed prior to the introduction of the NICE guidelines. Those guidelines have been welcomed by psychiatrists and patients, the majority of whom appear to favour the use of atypical over typical antipsychotics in schizophrenia treatment (Patel et al. 2003; Rethink (formerly known as the National Schizophrenia Fellowship) 2005). Of course, atypical antipsychotics are not homogeneous in their efficacy or side-effect profiles, and so comparisons within the atypical class of antipsychotics would be a useful topic for further research.

It is government policy in England to improve access to atypical antipsychotics, based on the evidence synthesis and consultations undertaken to inform the NICE review and guidance. Further evidence is needed to make more transparent the treatment choices being made by physicians. Variability in atypical prescribing rates, evidence of polypharmacy, and empirical

results such as those set out in this paper, indicating the use of non-need-based factors in antipsychotic drug choice, suggest that prescribing for schizophrenic patients retains elements of inconsistency and ambiguity.

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