STUDIES OF DEPRESSION AND ILLNESS REPRESENTATIONS IN
END-STAGE RENAL DISEASE

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Depression is a common psychopathology in patients with End-Stage Renal Disease that is associated with maladaptive illness representations. Moreover depression and illness representations predict adverse outcomes in End-Stage Renal Disease.
Abstract

Depression is a substantial psychopathology encountered in the dialysis population yet its association with potentially modifiable psychological antecedents are not well known. Of these potential antecedents, individual’s perception of their condition are likely to play an important role in how they adjust to their illness (Leventhal, Brissette, & Leventhal, 2003). The Common Sense Model suggests that illness representations guide the self-regulation of illness (Leventhal, Meyer, & Nerenz, 1980; Leventhal, Nerenz, & Steele, 1984). The model posits that the interpretation of illness (illness perceptions) influence the response and procedures adopted in order to regulate the illness threat. The overarching aim of the work here is to examine whether illness perceptions predict depression and its trajectory in End-Stage Renal Disease (ESRD) patients, and to establish if depression and illness perceptions are associated with adverse clinical outcomes in these patients.

In order to achieve these aims it was first important to establish how best to assess depression and illness representations in the context of ESRD. A pilot study investigated whether the Beck Depression Inventory (BDI) and the Revised Illness Perception Questionnaire (IPQ-R) could be administered to haemodialysis patients (HD) while actively on dialysis. Patients completed the BDI and IPQ-R while on-dialysis and again at a time when off-dialysis (n=40). Level of agreement revealed no discernable difference between BDI and IPQ-R scores across the two conditions, although there was a slight bias with regards to scoring on somatic items of the BDI while on-dialysis. Given these data, on-dialysis assessments were employed in the studies reported. Furthermore the BDI was compared against a diagnostic standard for Major Depressive Disorder (MDD) in order to define an adjusted BDI cut-off score that would indicate potential depressive cases. The data revealed that a BDI $\geq 16$ had optimal sensitivity and specificity for MDD. This cut-off score was employed to define patients with “probable” depression.

The factor structure of the BDI was the focus in the following chapter. BDI data from two larger studies (reported later in the thesis) were pooled in order to conduct confirmatory factor analysis, testing several proposed structures of the BDI. The analysis revealed that two and three factor solutions had relatively poor fit to the data. A relatively novel bi-factor model proposed by Ward (2006) had the best fit. In this model there is a general
depression factor that loaded onto all of the 21 BDI items, and two smaller orthogonal cognitive and somatic factors. These factors collectively explained 91% of the total variance in BDI-II total scores, suggesting that the BDI provides a good overall measure of global depressive symptoms.

The first study to examine the association between illness representations and depression was a cross-sectional study of established HD patients (n=215). Nearly 30% of the sample were depressed (BDI≥16), highlighting the extent of depressive symptoms in this patient group. Significant differences between depressed and non-depressed patients with regards to illness perceptions were evident. In logistic regression illness coherence, perceived consequences and treatment control perceptions predicted depression. Interestingly clinical variables including co-morbidity were unrelated to depression. This suggests that it is not disease severity or extra-renal co-morbidity per se that are vulnerabilities for depression, rather it is the interpretation of the disease that appears to be important.

The proceeding chapter extended this cross-sectional investigation by examining the trajectory of depression (i.e. change in depression) over the first year of dialysis therapy in relation to illness representations. An incident cohort of dialysis patients (n=160) were seen at a point soon after dialysis initiation and followed up 6 and 12 months thereafter. In particular, differences between patients who start dialysis via planned route (i.e. those with progressive renal failure who had been “worked-up” to dialysis) vs. those who started dialysis suddenly (unplanned starters) were sought. Unplanned starters were more depressed than the planned patients and held different illness perceptions. Structural equation modelling of the baseline data revealed that illness perceptions predicted depression, and that path to dialysis had an indirect effect on depression as mediated through illness perceptions. Over time, depression and illness perceptions appeared to remain relatively stable although there was some evidence of a non-linear decline in depression scores over the follow-up period. In addition, illness identity decreased over time, while illness coherence (understanding) increased. Clinical and demographic factors were not associated with the trajectory of depression as assessed using Latent Growth Models. However several illness perceptions were associated with a change in depression over time, suggesting that patient’s illness representations assist in the regulation (or under-regulation) of mood.
The first of two clinical oriented chapters examined the utility of illness representations in explaining fluid non-adherent behaviour. HD patients were categorised as either fluid adherent or non-adherent based upon Inter-dialytic Weight Gain (IDWG). Patients in the upper quartile of percent weight gain were defined as non-adherent (IDWG≥3.21% dry weight). The data revealed that non-adherent patients had lower timeline perceptions as compared to adherent patients. Logistic regression models were evaluated in order to identify predictors of fluid non-adherence. After several demographic and clinical variables had been controlled, lower consequence perceptions predicted non-adherence. This data points to the utility of understanding dialysis patient’s personal illness representations in relation to maladaptive health care behaviour.

Finally, the potential association between depression, illness representations and short term survival in incident dialysis patients was evaluated. Patients were followed up for a mean of 545 (±271) days in which there were 27 deaths (16.9%). Patients were censored if they were lost to follow-up, transplanted or recovered renal function. In Cox survival models after controlling for several co-variates including co-morbidity, depression significantly predicted mortality. Furthermore, survival models including illness perceptions revealed that treatment control perceptions were also predictive of mortality. These results suggest that depression and beliefs surrounding treatment control contribute to the survival of dialysis patients. Possible explanations regarding these associations are presented.

In conclusion the empirical investigations offered here support the thesis that illness perceptions predict depression in dialysis patients. Moreover there is evidence that illness representations are associated with maladaptive health behaviour (non-adherence) in dialysis patients. Depression and illness representations also predict short-term survival in incident patients after adjusting for important co-variates. Recent studies have shown that altering maladaptive illness perceptions via psychological intervention can have a positive influence upon outcomes (Petrie, Cameron, Ellis, Buick, & Weinman, 2002). Given the evidence presented in this thesis, testing interventions that target maladaptive illness representations in order to improve clinical and psychological outcomes seem highly relevant in this setting.
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Abbreviations

**BDI**: Beck Depression Inventory

**C**: Cognitive factor

**CA**: Cognitive Affective factor

**CBT**: Cognitive Behavioural Therapy

**CES-D**: Center for Epidemiologic Studies Depression Scale

**CDI**: Cognitive Depression Index

**CHD**: Coronary Heart Disease

**CKD**: Chronic Kidney Disease

**CFA**: Confirmatory Factor Analysis

**CFI**: Comparative Fit Index

**CI**: Confidence Interval

**CRP**: C-Reactive Protein

**CSM**: Common Sense Model

**CVD**: Cardiovascular Disease

**DIS**: Diagnostic Interview Schedule

**DF (df)**: Degrees of Freedom

**DOPPS**: Dialysis Outcomes and Practice Patterns Study

**DSM**: Diagnostic and Statistical Manual of Mental Disorders

**ESRD**: End-Stage Renal Disease

**EFA**: Exploratory Factor Analysis

**G**: General Depression Factor
**GFR**: Glomerular Filtration Rate

**G-S-C**: General-Somatic-Cognitive model

**HADS**: Hospital Anxiety Depression Scale

**Hb**: Haemoglobin

**HD**: Haemodialysis

**HDF**: Haemodiafiltration

**HR**: Hazard Ratio

**ICD-10**: International Classification of Diseases (ICD)

**IDWG**: Inter-Dialytic Weight Gain

**IL**: Interleukin

**IPQ**: Illness Perception Questionnaire

**IPQ-R**: Illness Perception Questionnaire Revised

**IQR**: Inter-Quartile Range

**KDQOI**: Kidney Disease Outcomes Quality Initiative

**KPS**: Karnofsky Performance Scale

**KRU**: Residual Renal Function

**LoA**: Level of Agreement

**LGM**: Latent Growth Model

**MDRD**: Modification of Diet in Renal Disease Study

**MDD**: Major Depressive Disorder

**MI**: Myocardial Infarction

**M.I.N.I**: Mini International Neuropsychiatric Interview
**ML:** Maximum Likelihood

**MMSE:** Mini Mental State Examination

**NC:** Noncognitive factor

**OR:** Odds Ratio

**PD:** Peritoneal Dialysis

**QoL:** Quality of Life

**RA:** Rheumatoid Arthritis

**RLS:** Restless Leg Syndrome

**RMSEA:** Root Mean Square Error of Approximation

**RR:** Relative Risk

**S:** Somatic factor

**SF-36:** The Short Form (36) Health Survey

**SCID:** Structured Clinical Interview for Depression

**SD:** Standard Deviation

**SE:** Standard Error

**SEM:** Structure Equation Model

**SA:** Somatic Affective factor

**SV:** Somatic Vegetative factor

**TLI:** Tucker Lewis Index

**TNF-α:** Tumor Necrosis Factor-alpha

**WLSMV:** Weighted Least-Squares with Mean and Variance Adjustment
PhD Related Publications


Submitted-

Chilcot, J., Wellsted, D., Davenport, A., Firth, J., Farrington, K (2010). Depression is an independent predictor of short-term survival in incident dialysis patients. *Submitted*

*Other Related Papers-*

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Prelude

Thesis Structure

In order to defend the thesis offered here the following empirical works are organised into three main sections. Following introductory review chapters surrounding the topics of End-Stage Renal Disease, depression in renal failure and the self-regulation of illness (illness representations), the first of the empirical sections is presented and concerns the consideration of the applied methodology. Specifically attention is devoted to the measurement of depression via the Beck Depression Inventory in the context of End-Stage Renal Disease. This work includes examining the procedure of on-dialysis depression screening and examining the psychometric properties of the Beck Depression Inventory.

The second empirical section concerns the relationship between depression and illness representations in two studies of dialysis patients. The first describes this association in a large cross-sectional sample of established haemodialysis patients. The second study addresses the longitudinal relationship between depression and illness representations in an incident sample of dialysis patients, examining changes in depression and its predictors over the first year of therapy.

The final empirical section presents two clinically focused studies. The first of which evaluates the utility of understanding illness representations in relation to maladaptive health behaviours (fluid non-adherence). The second study of this clinical section examines the association between depression, illness representations and mortality in incident dialysis patients.

The following introductory chapter concerns a basic overview of the kidneys, renal failure and dialysis. The aim of this introductory chapter is to describe the nature, consequences and treatment of kidney failure in preparation for the empirical works that investigate the psychological aspects of End-Stage Renal Disease. This introduction does not seek to provide an exhaustive account of advanced kidney disease and its management, but rather to define the population of patients with ESRD and to identify the major consequences of the condition.
Chapter 1

An Introduction to End-Stage Renal Disease

1.1 The Kidneys and Kidney Failure

The following introductory chapter is structured to provide an essential overview of the kidneys and their function. Furthermore, the consequences of renal failure and its treatment are considered. In addition, a brief description of the UK End-Stage Renal Disease population is provided.

There are two kidneys located retroperitoneally in the posterior part of the abdomen. Healthy kidneys weigh approximately 150g each, and are highly vascular receiving approximately 25% of the cardiac output. They are responsible for the maintenance of homeostasis, including the regulation of body fluid volume, maintaining electrolyte and acid-base balance, and excreting waste products including metabolic end-products such as urea and creatinine. The kidneys are also responsible for secreting and producing several enzymes and hormones, which regulate blood pressure (Renin), stimulate the formation of red blood cells (Erythropoietin, “EPO”), and regulate bone and mineral metabolism (1,25-dihydroxycholecalciferol – the active form of vitamin D). In healthy kidneys, these functions are carried out continuously.

The nephron is the functional unit of the kidney and has two main components, the renal corpuscle and renal tubules. The renal corpuscle acts as the initial filtering component, comprising of the glomerulus and Bowman’s capsule. The glomerulus is a capillary tuft that filters the blood under the influence of hydrostatic pressure. The glomerular filtrate is collected in the Bowman’s capsule and then processed and modified in the renal tubules, consisting of the proximal convoluted tubule, loop of Henle and the distal convoluted tubule. The complex functions of the tubules involve the regulated reabsorption of salt and water, and the selective reabsorption or secretion of many other substances. Over two thirds of the glomerular filtrate consisting of water, sodium, potassium, bicarbonate, amino acids, calcium, magnesium, phosphate and glucose are reabsorbed by the proximal convoluted tubules. This reabsorption is essential as the glomerulus filtrates 170-180 L of water and small molecules a day. The distal tubules are responsible for fine-tuning salt and water balance under the control of aldosterone and antidiuretic hormone (ADH). As a
consequence of this complex regulatory system, 1-2 litres of the filtrate are excreted per day as urine, removing excess fluid, toxins and metabolic end products from the body.

### 1.1.1 The Progression of kidney Failure (Chronic Kidney Disease)

Chronic Kidney Disease (CKD) refers to *kidney damage* or *reduced kidney function* which has persisted for a minimum period of 3 months (KDOQI, 2002). Kidney damage can be identified by renal biopsy, imaging the kidney (looking for structural abnormalities), or more typically via the detection of markers of kidney damage in the blood, such as the concentrations of urea and creatinine, and in the urine, such as the presence of blood and protein. Proteinuria is the presence of significant amounts of proteins such as albumin in the urine (albuminuria), and is regarded as a prominent marker of *kidney damage* (Keane & Eknayan, 1999). Microalbuminuria refers to the excretion of excess albumin in the urine, yet in levels below the detection limit of standard dipsticks tests.

The best *overall* measure of *kidney function* is glomerular filtration rate (GFR- Smith, 1951). GFR is defined as the volume of fluid filtered from the glomerular capillaries into the Bowman’s capsule per unit of time (mL/min/1.73m$^2$). GFR is dependent upon several factors including age, sex and body size. A GFR of 120-130 mL/min/1.73m$^2$ is considered normal in healthy adults, though this declines with age (Rowe, Andres, Tobin, Norris, & Shock, 1976; Smith, 1951). The gold-standard measure of GFR is Inulin clearance which involves an intravenous infusion and precisely timed urine collections. Inulin is a small molecule that is easily filtered through the glomeruli with no re-absorption in the renal tubules. However, Inulin clearance is rarely used in clinical practice because it is time-consuming and costly. Alternative methods including the urinary excretion of exogenous radioactive markers such as $^{125}$I-iothalamate and $^{99m}$Tc-DTPA (Perrone et al., 1990) and plasma clearance of exogenous substances (Cr-EDTA) are also reliable measures of GFR (KDOQI, 2002). These methods are also costly and are more appropriate in a research environment rather than tools for use in clinical practice. Creatinine clearance is another method of estimating GFR, which is more applicable to clinical practice. This requires a 24 hour urine collection and an estimate of creatinine concentration in the serum.
Creatinine clearance is defined by the following formula:

**Creatinine Clearance (mL/min) = U x V/P,**

where $U$ = urine concentration of creatinine; $V$ = urine flow rate (mL/min) and $P$ = plasma concentration of creatinine. Creatinine is a small molecule resulting from the metabolic break down of creatine phosphate found in muscle. Creatinine is a middle sized molecule freely filtered by the glomerulus, with little re-absorption in the renal tubules. Elevated levels of serum creatinine (>120 μmol/l) suggest renal impairment. Serum creatinine is affected by factors other than GFR, such as muscle bulk and protein intake, thus there is variation of serum creatinine both in patients with normal and impaired kidney function. Furthermore serum creatinine concentration does not rise out of the normal range until around 50% of GFR is lost. Hence serum creatinine alone is insufficient to determine the severity of kidney function. In addition, **creatinine clearance** estimations generally overestimate GFR due to tubular secretion of creatinine. Variation of laboratory techniques for creatinine estimation, and inaccurate 24 hour urine collections are additional problems with this methodology. As a result of these issues, estimates of GFR are commonly used in clinical practice. These are derived from predictive equations. The two most common equations are; the Cockcroft-Gault equation (Cockcroft & Gault, 1976) and the Modification of Diet in Renal Disease (MDRD) study equation (Levey et al., 1999), which are defined below:

**Cockcroft-Gault equation:**

$$\text{Creatinine Clearance (mL/min)} = \left(\frac{140 - \text{Age} \times \text{Weight}}{72 \times \text{Serum Creatinine}}\right) \times 0.85$$

if female

**Abbreviated 4 variable MDRD equation:**

$$e\text{GFR} \text{ (ml/min/1.73m}^2\text{)} = 186 \times [\text{Serum Creatinine}]^{-1.154} \times [\text{Age}]^{-0.203} \times [0.742 \text{ if female}] \times [1.21 \text{ if black}].$$

where $e\text{GFR}$ is estimated GFR, age is measured in years, weight in kg, serum creatinine in mg/dL. The MDRD equation was validated against the urinary clearance of $^{125}\text{I}$-iothalamate (Levey et al., 1999). It is generally preferred for routine clinical use, since it does not require
the input of body weight, which is usually not available at the point of estimation by clinical laboratories.

Renal failure can follow either an acute or chronic course. Acute Kidney Injury (AKI) is the loss of renal function in a setting in which the loss is potentially reversible. The onset of AKI is usually sudden with a time course of hours or days. CKD is the progressive deterioration of renal function resulting in irreversible kidney damage. CKD is defined by either of the following: 1) Kidney damage as evident by markers (e.g. proteinuria) or structural abnormalities with normal eGFR, for a minimum of three months, or 2) GFR<60 mL/min/1.73m² for greater than three months (KDOQI, 2002). CKD is classified according to the severity of renal impairment as measured by eGFR (table 1.1). Stage 3 reflects significant renal impairment and identifies individuals with CKD. It is from this point that the complications of CKD become more apparent, which are discussed later. eGFR falls with age and many patients with stage 3 CKD do not have progressive disease. The presence of proteinuria is a good marker of the likelihood of progression. Many patients with stage 4 CKD (GFR<30 mL/min/1.73 m²) have progressive disease, and preparation for renal replacement therapy is often usually appropriate. Stage 5 CKD is referred to End-Stage Renal Disease (ESRD) or Established Renal Failure (ERF). In ESRD survival is limited without the initiation of renal replacement therapy (RRT).

### Table 1.1: Stages of renal failure according to eGFR

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (ml/min/1.73m²)</th>
<th>Functional Description</th>
<th>Prevalence (%)~</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>Kidney function normal, but indication of underlying disease due to an abnormality</td>
<td>3.3</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Mild loss of kidney function, or other abnormality</td>
<td>3.0</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>Moderately reduced function</td>
<td>4.3</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severely reduced function</td>
<td>0.2</td>
</tr>
<tr>
<td>5</td>
<td>≤14</td>
<td>End-Stage Renal Disease (ESRD)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

~prevalence estimates based upon NHANES III data (Coresh, Astor, Greene, Eknoyan, & Levey, 2003)
1.1.2 Factors that affect the progression of CKD

In progressive CKD data from the MDRD study suggests that GFR declines on average by 4ml/min/year, a rate unrelated to baseline GFR (Hunsicker et al., 1997). However, as identified in a review by the National Kidney Foundation, the rate of GFR decline is varied across studies (0 – 12ml/min/year). The rate of decline can be used to estimate the onset of ESRD, although this can be challenging. A rate of GFR loss of >4 ml/min/year is considered “fast” according to current guidelines (KDOQI, 2002).

Despite the variations among the literature, several factors have been shown to impact upon the progression of CKD (KDOQI, 2002);

- The degree of proteinuria
- Blood pressure control
- Glucose control in diabetes
- Angiotensin-converting enzyme inhibition or angiotensin-2 receptor blockade

Diabetes is the most common cause of ESRD (USRDS, 2003). Indeed, the rise in ESRD prevalence rates over the past 10 years is partially attributable to the growing incidence of diabetes (USRDS, 2003). The evidence regarding the benefit of strict glucose control upon preventing or slowing the progression of kidney disease is robust (DCCT, 1993; MACSG, 1995; UKPDS, 1998a). Data from the Diabetes Control and Complications Trail randomised type 1 diabetics to either a conventional treatment group, or a intensive glucose control group (DCCT, 1993). The intervention group received insulin more than three times per day in order to maintain normal HbA1c levels. The standard treatment group received insulin once or twice per day. Patients were followed up for an average of 6.5 years. Albuminuria (protein leak) was employed as the outcome measure, which indicates nephropathy (kidney damage). Patients were also grouped according to the presence of mild retinopathy (damage to retinal blood vessels as a result of high blood sugars). A primary prevention group had no retinopathy at baseline n= 726, whilst a secondary prevention group had retinopathy at baseline n=715.
The data revealed the benefits of intensive therapy upon the subsequent protection against albuminuria (figure 1.1). For patients in the primary prevention cohort, intensive therapy reduced the adjusted risk of microalbuminuria by 34 percent. For the secondary prevention cohort, intensive therapy reduced the risk of microalbuminuria and albuminuria by 43 and 56% respectively (p=0.01).

Although this data does not show that tight glucose control prevents GRF loss *per se*, it does demonstrate that increased control protects against kidney damage. In addition, an elegant analysis conducted by the United Kingdom Prospective Diabetes Study showed that strict glycemic control had a significant impact upon the prevalence of microalbuminuria and reduced the incidence of declining renal function, as compared to standard therapy (UKPDS, 1998a).

High blood pressure is known to cause kidney disease. Evidence also suggests that poorly controlled blood pressure is a prognostic factor for declining kidney function (Levey et al., 1998). The largest study of blood pressure control in patients with non-diabetic kidney disease comes from the MDRD research group (Klahr et al., 1994). Patients were
randomised to either a standard treatment group (target blood pressure <140/90 mm/Hg), or the strict blood pressure control intervention group (<125/75 mm/Hg). The results revealed that the intervention group had a significantly slower rate of progression of CKD, but only in patients who had proteinuria >1.0g/d, as compared to the standard treatment group. The benefit of tight blood pressure control in type 2 diabetics has also been established with data showing that better control is associated with reduced microalbuminuria (UKPDS, 1998b).

The degree of proteinuria is the major determinant of progression in CKD irrespective of aetiology. Angiotensin-converting enzyme inhibition (ACE inhibitors) and Angiotensin II receptor blockade (ARBs) have been shown to slow the progression of renal failure in both diabetic and non-diabetic renal disease. The specific benefits of these agents over and above standard antihypertensive agents are essentially limited to their use in proteinuric states (syndrome cause by renal impairment indicated by blood and protein in the urine). These medications disrupt the Renin-Angiotensin Aldosterone System by inhibiting the production of angiotensin II (ACE inhibitors) or it’s interaction with its receptors (ARBs). Angiotensin II modulates intraglomerular capillary pressure, and causing increased glomerular hydraulic pressure. Blocking or inhibiting this system via the use of ACE inhibitors of ARBs serves to protect glomerular filtration, by preventing hyperfiltration, cell proliferation and fibrosis (Weir & Dworkin, 1998). In addition to this effect, ACE inhibitors and ARBs reduce blood pressure and have antiproteinuric properties (Ruggenenti & Remuzzi, 1997). Studies have shown that in type 1 diabetics with normal blood pressure, ACE inhibitors slow CKD progression (Lewis, Hunsicker, Bain, & Rohde, 1993). A meta-analysis of trials in non-diabetic patients has also provided evidence for the efficacy of these drugs. This data revealed that patients receiving ACE-inhibitors had lower urine protein excretion, improved blood pressure control, and approximately a 30% reduction in the risk of development of kidney failure, as compared to the control group (Jafar et al., 2001).

In addition to tight glucose control, blood pressure management and the administration of ACE-inhibitors or ARBs other factors may also be important. Restricting protein intake,
reducing lipids and correcting anaemia are several interventions that may slow the progression of CKD, although evidence is contentious (KDOQI, 2002).

1.1.3 The consequences of CKD

Early stages of renal impairment may be asymptomatic. Various “uraemic” symptoms can result from severe renal failure, though this is difficult to define in purely biochemical terms (table 1.2). The adverse consequences of CKD typically start to manifest once GFR<30 mL/min/1.73 m² (i.e. Stage IV CKD). Anaemia is a common consequence of CKD. The kidneys produce the hormone Erythropoietin, with is essential for Erythropoiesis (production of red blood cells). In kidney failure there is Erythropoietin deficiency causing anaemia. Haemoglobin (Hb) is the preferred method of assessing anaemia, although there is no CKD specific definition (KDOQI, 2002). Current guidelines recommend that Hb levels should be in the range of 10.5-12.5 g/dL for patients with CKD. Evidence suggests that anaemia progresses with CKD (Levin et al., 1999; McGonigle, Wallin, Shadduck, & Fisher, 1984). For example, in the USA it is estimated that 1.2 million women and 390,000 men have Hb< 12.0 g/dL that is associated with CKD (Hsu, McCulloch, & Curhan, 2002). Data from the Third National Health and Nutrition Examination Survey (NHANES III) demonstrated a decline in Hb with falling eGRF (figure 1.2). Although anaemia is strongly associated with a GFR<60 ml/min/1.73 m², there is also evidence of anaemia with higher levels of GFR (KDOQI, 2002). Anaemia is associated with negative outcomes including, increased mortality risk, hospitalisation, cardiovascular disease and reduced quality of life (Collins, Ma, Xia, & Ebben, 1998; Foley et al., 2000; Furuland et al., 2003; Levin & Foley, 2000).

Renal osteodystrophy is another complication of CKD caused by reduced renal activation of vitamin D, phosphate retention, lower ionized calcium and increased parathyroid hormone (PTH). CKD patients experience several forms of bone disease, with most having mixed bone diseases, including hyperparathyroidism and adynamic bone disease. Other issues relate to skin diseases (itching), endocrine abnormalities, gastrointestinal complications, and damage to the nervous system.
Table 1.2: Symptoms of CKD (Uraemia)

<table>
<thead>
<tr>
<th>Symptoms of CKD</th>
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<tbody>
<tr>
<td>Loss of energy</td>
</tr>
<tr>
<td>Vomiting, diarrhoea, and nausea</td>
</tr>
<tr>
<td>Mental slowing, seizures*</td>
</tr>
<tr>
<td>Loss of appetite</td>
</tr>
<tr>
<td>Peripheral or pulmonary oedema</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Nocturia</td>
</tr>
<tr>
<td>Rest leg syndrome- need to</td>
</tr>
<tr>
<td>Anaemia related symptoms –</td>
</tr>
<tr>
<td>continuously move lower limbs</td>
</tr>
<tr>
<td>fatigue, pallor, tachycardia,</td>
</tr>
<tr>
<td>palpitations</td>
</tr>
<tr>
<td>Paraesthesiae</td>
</tr>
<tr>
<td>Bone pain</td>
</tr>
<tr>
<td>Amenorrhea</td>
</tr>
</tbody>
</table>

*typically associated with serve uraemia

Figure 1.2: Blood haemoglobin percentiles by GFR adjusted to age 60 (NHANES III). Median and 5th and 95th percentiles of haemoglobin among adult participants age 20 years and older in NHANES III, 1988 to 1994. Values are adjusted to age 60 years using a polynomial quantile regression. The estimated GFR for each individual data point is shown with a plus sign near the abscissa. 95% confidence intervals at selected levels of estimated GFR are demarcated with triangles, squares, and circles. Reproduced with permission from the American Journal of Kidney Diseases (KDOQI, 2002).

The most significant complication of kidney failure is cardiovascular disease (CVD). Dialysis patients are 10-30 times more likely to die of CVD compared with the general population after controlling for sex, race, and diabetes (Foley, Parfrey, & Sarnak, 1998). Controlling for age still leaves a 5 fold increase in CVD mortality. Features of CVD including left ventricular hypertrophy (LVH) and atherosclerosis are significantly more prevalent among patients
receiving haemodialysis (Foley et al., 1995). LVH appears to develop early in the course of
CKD, affecting around 38% of CKD stage 4 patients. At dialysis initiation around 70% of
patients have LVH (Foley et al., 1995), which is a significant independent predictor of
mortality among dialysis patients (Silberberg, Barre, Prichard, & Sniderman, 1989). Vascular
calcification, including coronary artery calcification, is another significant concern among
patients with kidney failure. Conventional risk factors associated with the development of
accelerated atherosclerosis, and renal failure specific risk factors relating mainly to
abnormal mineral metabolism and its treatment, both contribute. Coronary artery
calcification is common among dialysis patients and remains a significant independent
predictor of all cause mortality among dialysis patients (London et al., 2003).

1.2 The treatment of End-Stage Renal Disease
The treatment of kidney failure essentially involves attempts to prevent or to manage the
consequences of impaired renal function. As renal failure progresses dietary modification
and specific medications are required but when ESRD is reached renal replacement therapy
become a necessary addition to this regime.

For example, hyperkalaemia (high serum potassium >5.5 mmol/l) is generally treated by
diet modification although levels greater than 7 mmol/l often present as medical
emergencies requiring specific treatment. Dietary limitations are required to maintain
adequate potassium levels, often involving specialist advice from renal dieticians. Similarly,
phosphate control is regulated by dietary control and the ingestion of phosphate binder
medications. Metabolic acidosis (acidification of blood where pH<7.35) is corrected by
dialysis (using bicarbonate, described below). Anaemia is corrected by the maintenance of
adequate haematinics and the administration of biosynthesized erythropoietin (EPO). This
is normally administered by subcutaneous injection in the predialysis setting, though the
intravenous route is often preferred for haemodialysis patients. EPO administration is
associated with many benefits including improved quality of life, sexual and cognitive
function. Most of these clinical aspects of management continue to require rigorous
attention even after patients have initiated renal replacement therapy.

The control of blood pressure by dietary sodium restriction and antihypertensive
medication is also a major aspect of predialysis management, which persists into the renal
replacement therapy phase. In fact, once dialysis has commenced, these and other management strategies, usually become more intrusive. With continued loss of residual renal function most dialysis patients eventually lose their urine output. In this setting, while dialysis is capable of removing some excess salt and water, the patient is required to restrict their salt and water intake more rigorously – with fluid intake usually limited to 0.5-1 litres/daily. If patients ingest too much salt and water, they become “overloaded” and risk complications such as pulmonary oedema and congestive heart failure. Such complications require hospitalisation and can prove fatal. Fluid intake restriction is a particular a frustration to the patient. Indeed fluid non-adherence has been identified as a particularly prevalent issue (Bame, Petersen, & Wray, 1993).

1.2.1 Renal Replacement Therapy
Dialysis is the most common form of renal replacement therapy (Grassmann, Gioberge, Moeller, & Brown, 2005). Essentially, dialysis replaces some renal function acting as an artificial kidney. Dialysis allows small and middle sized-molecules to be removed from the blood (e.g. metabolic end-products), whilst also removing fluid. There are two basic types of dialysis, Haemodialysis (HD) and Peritoneal Dialysis (PD). Both modalities essentially serve the same purpose but differ in their application.

1.2.2 Haemodialysis
HD is typically conducted in a hospital or clinic, for 3-4 hours thrice weekly. Essentially blood is removed from body, filtered and then returned to the patient. An Arteriovenous Fistula (AV fistula) is the preferred method of access. An AV fistula is fashioned surgically. A subcutaneous vein – usually at the wrist or elbow is joined to a suitable artery. This causes the vein to increase in diameter and “arterialize” – allowing frequent puncturing for dialysis access. Two needles are inserted in the fistula at each dialysis session, one in which the blood leaves the body to circulate around the machine and dialyzer (“A” needle), and the other through which the blood returns (“V” needle). The dialyser consists of a semi-permeable membrane separating the patient’s blood and the dialysis fluid. Membranes vary in permeability, high-flux membranes permitting good removal of larger molecular weight toxins such as beta-2-microglobulin (i.e. middle sized molecules) in contrast to low-flux membranes which only permit removal of low molecular weight substances. The blood
and the dialysis fluid are pumped through the dialyser in a countercurrent fashion to maximise concentration gradients. HD works by the principles of convection and diffusion. Waste products are mainly removed by diffusion down the concentration gradient between the blood and the dialysis fluid. The composition of the dialysis fluid is devised to optimise the removal of toxins and excess minerals and electrolytes, such as potassium and magnesium, prevent excess removal of sodium, and to allow acidosis to be corrected by infusion of bicarbonate. Fluid is sucked from the blood into the dialysis fluid by convection, brought about by application of a negative pressure to the dialysis fluid side of the membrane. Convection also facilitates the removal of middle molecules.

Dialysis systems have been devised which maximise convection, and require infusion of replacement fluids into the patient (haemodiafiltration). This allows a modest improvement in small molecule clearance and a significant improvement regarding middle molecule clearance compared to high flux haemodialysis. Empirical evidence suggests that HDF may improve haemodynamic stability and mortality rate (Canaud et al., 2006).

Haemodialysis adequacy is assessed by either the urea reduction ration (URR) of normalised urea clearance (Kt/V, where K is the dialyser clearance, t is the duration of the dialysis treatment in minutes and V is the urea distribution estimated by total body water). A sessional URR of >65% or Kt/V of 1.2 is the target adequacy for haemodialysis (KDOQI, 2002). These adequacy criteria relate to thrice weekly treatments, which are currently the norm, though significant benefits may accrue from more frequent sessions.

Haemodialysis can take place in-centre, in minimal care units or in the home. In centre-based therapy, nurses or health care assistants undertake most of the work associated with the treatment. In minimal care units patients are responsible for most of their treatment. In home haemodialysis, the patient with or without a carer assumes all responsibility for the day-to-day performance of the treatment. In-centre treatment is by far the most common current means of dialysis delivery. The majority of patients studied in the following chapters were receiving in centre-based treatment usually by high-flux haemodialysis with a smaller number receiving Haemodiafiltration.
1.2.3 **Peritoneal Dialysis**

Peritoneal dialysis (PD) removes metabolic end products and fluid from the body via a naturally occurring semi-permeable membrane. This refers to the peritoneal membrane which lines the peritoneal cavity and surrounds the intestine. PD requires the insertion of a peritoneal catheter (Tenckhoff catheter) into the patient’s abdomen. Dialysis fluid is then introduced into the peritoneal cavity. The same principles of diffusion and convection as described above also operate in peritoneal dialysis, except that convection now occurs down an osmotic gradient created by high concentrations of glucose in the dialysis fluid. Peritoneal dialysis is a home-based treatment. Continuous ambulatory peritoneal dialysis (CAPD) is typically conducted throughout the day and involves four dialysis exchanges. Automated Peritoneal Dialysis (APD) involves the patient dialyzing at night, with a machine managing the exchanges over an 8-10 hour period. The self-care aspect associated with PD tends to mean that this modality is generally suited to younger patients with less co-morbidity, though older independent patients may also do well on this modality (Brown, 1999; Brown et al., 2010). Of the potential complications associated with PD peritoneal infection is a prominent concern. It usually responds to antibiotics but in rare cases may be fatal.

1.2.4 **Transplantation**

Renal transplantation if the preferred treatment for ESRD, though only a minority of patients are suitable. This reflects the increasing age and co-morbid load of the ESRD population. A successful transplant often reverses some of the complications induced by kidney failure, including anaemia and infertility. Furthermore, the need for tight dietary and fluid restriction is no longer required. Transplantation involves the donation of a kidney either from a living related donor or a “brainstem dead” or “non-heart-beating” donor (cadaveric). The benefits of renal transplantation are well established, improving both survival and quality of life. However the demand for donor kidneys outweighs the supply, which prolongs patient’s reliance upon dialysis therapies. Successful transplantation generally relies upon matching blood group antigens, though exceptions are increasingly common. HLA matching may improve outcomes but mismatching is generally not a barrier. Following a transplant, immunosuppressive medication is required for the duration of the
transplant. Advances in this regard have led to transplanted kidney surviving longer, with around 50% lasting 10 years or more.

1.3 Referral to a nephrologist and when to start dialysis

Referral to nephrologist for specialist assessment should typically occur once GFR = <30ml/min/1.73 m². Renal disease can remain asymptomatic for some individuals until the disease is very advanced. These individuals then present to nephrology services in need of urgent dialysis. Such patients are often termed “crash-landers.” Other patients may have been seen in primary or secondary care with known kidney disease yet for some reason are delayed before referral to a nephrologist (“late referral”). Further, patients may have been referred and clinically assessed by a nephrologist, but go on to need dialysis far sooner than initially expected (“failed planned”). These several pathways to dialysis initiation are all characterised by a sudden start to dialysis. Starting dialysis within 90 days of referral to a nephrologist is often used to define “late presenters,” although there is no accepted definition. For the purpose of this body of work, such patients are termed “unplanned starters”. In comparison to unplanned starters, most patients start dialysis via a planned entry (approximately 80%). This implies that patients were referred to a nephrologist when their GFR was around 30 ml/min/1.73 m², and were followed up over a period of time (usually many months or years), until a treatment decision was decided. Critically, these patients had time to adapt, seek support and to be educated. Such patients are termed “planned starters” in the work to follow. An unplanned start to dialysis has been shown in several empirical works to have adverse consequences upon patient outcome (Arora et al., 1999; Innes, Rowe, Burden, & Morgan, 1992).

Selecting a point at which point to start dialysis therapy is a complicated issue with no definitive answer. Dialysis is currently started when eGFR is at a mean of around 7-8 ml/min/1.73 m². KDQOI guidelines recommend considering starting dialysis when GFR <15 ml/min/1.73 m², whereas the Renal Association (UK) guidelines recommend dialysis consideration when GFR <10 ml/min/1.73 m². The need to initiate dialysis can also be indicated by a variety of clinical features including symptoms of uraemia, fluid overload, and nutritional status. These features tend to be more important indicators of the need for dialysis than the eGFR.
There is little debate about the survival disadvantage of late referral, but whether starting dialysis early confers any survival advantage is still controversial. Data from the Netherlands Cooperative Study on the Adequacy of Dialysis suggests that a prompt dialysis start defined by a GFR>10 ml/min/1.73 m$^2$ confers a survival advantage after 3 years on dialysis of 2.5 months (Korevaar et al., 2001). This advantage was explained in terms of treating patients at an earlier stage of the disease (i.e. before ESRD) hence there is potential lead-time bias (Korevaar et al., 2001).

1.4 The incidence of ESRD in 2007 - Data from the UK Renal Registry

The UK Renal Registry (http://www.renalreg.com) was developed by the renal community (The Renal Association) as a resource to improve patient care. The registry collects standardised data from all UK renal services quarterly, relating to incidence, clinical outcomes and management of CKD.

Data from the UK Renal Registry shows that in 2007 6,644 patients started renal replacement therapy (Farrington, Udayaraj, Gilg, & Feehally, 2008). Indeed over the last 17 years the incidence for RRT has increased progressively (figure 1.3).

![Figure 1.3: UK Renal Replacement Therapy incident rates from 1990-2007.](image-url)
In the 2007 incident dialysis cohort the median age was 64.1, with the majority of patient being male (61.8%). The acceptance rate was highest for both males and females for patients aged between 75-79 years of age (figure 1.4). The majority of incident patients were white (79.8%, Asian 10.0%, Black 7.3%, Chinese 0.6%, and other 2.3%). Diabetic nephropathy accounted for the most common diagnosis in incident patients (21.9%), followed by glomerulonephritis (10.7%), renal vascular disease (7.4%), pyelonephritis (7.1%), polycystic kidney disease (7.1%), and hypertension (5.8%). Other causes and unknown aetiology accounted for 15.1% and 25.0% of cases respectively.

HD was the most common treatment undertaken at the very start of dialysis (<90 days, 74.9%), compared to PD (20.6%) and pre-emptive renal transplant (4.5%). This data is somewhat biased as most patients who present late (late referrals and crash-landers) start on HD. The established modality by 90 days was; HD (64.7%), PD (21.3%), pre-emptive renal transplant (5.2%), died (5.7%), and stopped treatment (0.5%). There were no significant gender differences between those who start on HD and PD, although age was a significant factor. Older patients (≥65 years) were more likely to start on HD as compared to PD (82.7% vs. 17.3%). Figure 1.5 shows the time of referral before dialysis initiation. Twenty one percent of dialysis patients started treatment as a late presenter (unplanned starter).
Renal registry data of incident dialysis patients between the years 2002-2007, revealed several differences between planned and late presenting patients (Farrington, Udayaraj et al., 2008). Late presenters were significantly older and more likely to be white. In addition, fewer late presenters had “no co-morbidities” as compared to planned patients. Specifically, there was a significantly greater prevalence of malignancy in the late presenters as compared to the planned patients. Estimated GFR was significantly lower in the late presenting patients as compared to planned patients.

1.5 The prevalence of ESRD- Data from the UK Renal Registry

Between the years 2000-2007 the prevalent RRT population has grown by 40% (5%/year). According to the UK renal registry 45,484 patients were undergoing RRT in 2007 (Farrington, Hodsman, Casula, Ansell, & Feehally, 2008). Of these, 19,706 were treated with HD, 4,646 with PD and 21,132 with a renal transplant. The mean age of the HD and PD populations were 65.2 years and 60.3 years respectively. The mean age for transplant patients was notably younger at 50 years of age. The overall UK peak crude prevalence rate (correcting for the age and gender distribution of the UK) occurred in the age band 70–74. The crude prevalence rate for males was greater than females across all ages (figure 1.6).

Figure 1.5: Time of referral before dialysis initiation from the 2007 incident cohort. Data from Farrington et al (2008).
The median treatment vintage for HD patients was 2.8 years. PD and transplant patients had median vintages of 2.1 and 10.4 years respectively. The majority of established RRT patients were white (65.3%). Glomerulonephritis (biopsy proven) was the most common diagnosis (15.3%), followed by diabetes (13.2%) and pyelonephritis (11.9%). Unknown aetiology and other causes remained high accounting for 21.6% and 14.5% of the RRT population.

Among the prevalent UK RRT population in 2007 renal transplant was the most common modality (46.6%) followed by HD (42.1%) and PD (10.1%). Analysis of treatment modality via age (<65 years vs. ≥65 years) suggests that age is a strong determinant of modality. Of the prevalent HD population 66.4% were aged ≥65 years, compared to only 11.9% of the PD population and 21.6% of the transplant population.
1.6 Summary

The kidneys serve to maintain fluid balance and body homeostasis. Kidney disease reduces the functionality of the nephron, signified by low GFR. Renal failure is associated with high mortality, particularly related to cardiovascular disease. In order to replace the functions of the kidney, dialysis or transplantation is required, with transplantation offering the better quality of life. In order to maintain life, regular dialysis is required for as long as the patient lives. However the dialysis is only one aspect of the treatment regime. Dietary and fluid restrictions are also required, accompanied by an extensive list of medications. These self-care behaviours are critical to the management of ESRD. The chronic nature of ESRD, associated complications, and life restrictions have a sizeable effect upon the lives of sufferers. Indeed, patients are required to self-regulate not only health related behaviour but also mood. As reviewed in the following chapter, ESRD and its treatment is associated with depression, which remains a significant co-morbidity in this population. Further because ESRD is a complex disease understanding patient’s common sense representations of their condition may help provide a theoretical basis to the understanding of illness, mood and behaviour in this patient population.
Chapter 2

A Review of Depression on Dialysis

- “If you be sick, your own thoughts make you sick”

  Benjamin Jonson (1572-1637)

2.1 Introduction

The relationship between depression and physical illness is highly intimate. It is evident that depression, or sub-syndrome depressive disorders are implicated in both the aetiology and consequence of physical illness. Co-morbid depression has profound effects upon morbidity, mortality, self-care behaviour and health care costs in patients with chronic physical disease (Stein, Cox, Afifi, Belik, & Sareen, 2006). At any given time it is thought that 2 to 4% of the general population suffers from depression, rising to between 5 and 10% in primary care (Kessler et al., 2003). Among patients with ESRD the reported point prevalence of depression or significant depressive symptoms is estimated to be between 20-30% (Cukor, Coplan, Brown, Peterson, & Kimmel, 2008; Drayer et al., 2006; Kimmel & Peterson, 2005). However, the use of different depression assessment tools has lead to wide variation in estimated prevalence rates (Craven, Rodin, Johnson, & Kennedy, 1987; Craven, Rodin, & Littlefield, 1988; Smith, Hong, & Robson, 1985). Most notable regards the difference between estimates based upon screening questionnaire cut-off scores used to define “caseness” and clinical diagnosis. Furthermore, there are discrepancies in prevalence estimates between patients receiving HD and PD modalities, although methodological factors may contribute to this mixed evidence. Despite this depression is thought to be the most common psychopathology encountered in dialysis patients, the under recognition of which in day-to-day clinical practice is of considerable concern (Wang & Watnick, 2004). This concern is exacerbated by the growing body of empirical evidence identifying the adverse consequences of depression on clinical outcome in ESRD patients. In this chapter I

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1 To note, parts of this review chapter have been published in Chilcot, J., Wellsted, D., Farrington, K (2010). Depression in End-Stage Renal Disease: Current Advances and Research. *Seminars in dialysis* (23): 74-82.
review depression in the context of renal dialysis, consider the prevalence and associated adverse outcomes, treatment options, and the psychological and clinical correlates. First however, the thorny issue of assessing depression in physical illness is considered.

2.2 Assessing depression in ESRD: diagnosis, screening and overlapping symptoms

The assessment of depression in ESRD, and indeed among chronic illness states is challenging. Firstly, it is important to distinguish the diagnosis of depression from depression screening methods. Diagnostic approaches rely upon professional evaluation typically by structured or semi-structured interviews using diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders 4th edition - DSM-IV (APA, 1994). The DSM-IV defines Major Depressive Disorder (MDD) as having a loss of pleasure/loss of interest or depressed mood for 2 weeks accompanied by five or more psychological, somatic and behavioural symptoms. Sadness, loss of pleasure, a lack of energy, sleep disturbances, loss of concentration, intense guilt and thoughts of suicide are some of the symptoms associated with MDD. The Structured Clinical Interview for Depression (SCID) is one diagnostic assessment based upon the DSM-IV criteria. Other diagnostic methods included, the Diagnostic Interview Schedule (DIS). Formal diagnosis has implications for the management and treatment of depressive disorders. However as will be discussed, diagnostic criteria for depression among physical illnesses are complicated by the somatic symptoms of illness.

In contrast screening approaches lack diagnostic capability. Depression screening tools such as the Beck Depression Inventory (BDI and BDI-II) are typical self-report scales requiring the patient to rate symptom frequency or severity (Beck, Steer, & Brown, 1996; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). Such tools assess the patient’s mood based upon a continuum, with higher depression scores often reflecting greater depressive symptoms. Self-report scales like the BDI are useful research tools which allow depression to be quantified across a population who do, as well as those that do not meet diagnostic criteria for depression. Although screening tools are not diagnostic, several have been validated against diagnostic criteria. This involves assessing the sensitivity and specificity of a defined symptom cut-off score against a diagnosis of clinical depression. The suggested cut-off
score for the BDI in ESRD patients is between 14-16, which is higher than the original score of >10 (for BDI-IA) and ≥13 (BDI-II), proposed for the general population (Craven et al., 1988; Grant, Almond, Newnham, Roberts, & Hutchings, 2008; Hedayati, Bosworth, Kuchibhatla, Kimmel, & Szczech, 2006; Watnick, Wang, Demadura, & Ganzini, 2005). However caution is noted as different groups have used difference versions of the BDI (e.g. BDI-IA and BDI-II, see chapter 4). Furthermore although the employment of screening cut-off scores is widely used such methods do not have diagnostic properties; instead they serve to identity patients with significant depressive symptoms or to assess the severity of depression. The use of the BDI, its structure and validation, are discussed in detail in the general methods chapter (chapter 4) and in chapter 6. In addition the non-somatic BDI for use in renal patients (Cognitive Depression Index, CDI) will come under scrutiny (Sacks, Peterson, & Kimmel, 1990).

The cardinal issue concerning both screening and diagnostic methods is criterion contamination, which refers to the overlap between the physical symptoms of depression and those of illness. For example uraemia causes several symptoms that are also associated with depression including fatigue, sleep disorders, and reduced appetite (Israel, 1986). Other confounding symptoms include anaemia and electrolyte disturbances, which may produce symptoms similar to those of depression (Brown & Brown, 1995; Nissenson, 1989). The cause of such symptoms may be attributable to physical (or organic) factors, depression or indeed both. For these reasons many depression questionnaire cut-off scores are higher when applied to patients with chronic illness, as compared to psychiatric populations. It is inappropriate to use a depression screening tool to define probable “caseness” among physically ill populations unless the cut-off scores employed for such definitions have been derived from the population under investigation. Failure to adjust the score will lead to inflated estimates of depression (false positives). It is still important to remember that such cases do not translate into disorders, thus positive screens should be supported with diagnostic enquiry. Although adjusting cut-off scores attempts to control for the impact of physical symptoms on scoring and improves sensitivity and specificity, the higher order issues concern what to do with such symptoms when faced with diagnostic enquiry? According to the DSM-IV somatic symptoms that are judged to be caused by illness or its treatment should not be included in the diagnostic assessment, although there
is no specific guidance regarding this etiological procedure. This problem then relates back to the scrutiny of screening tools, which in order to demonstrate validity, are compared with apparent “gold-standard” diagnostic criteria.

**Table 2.1: A summary of the DSM-IV criteria for MDD and alternative schemas for physical illnesses.**

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Concept</th>
<th>Symptoms</th>
</tr>
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<tbody>
<tr>
<td>All approaches</td>
<td>Core symptoms</td>
<td>- Dysphoric mood</td>
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<tr>
<td></td>
<td></td>
<td>- Loss of interest or pleasure</td>
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<td></td>
<td></td>
<td>- Psychomotor agitation/retardation</td>
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<tr>
<td></td>
<td></td>
<td>- Feelings of worthlessness/guilt</td>
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<tr>
<td></td>
<td></td>
<td>- Recurrent thoughts of death/suicide</td>
</tr>
<tr>
<td>DSM-IV (etiological)</td>
<td>Symptoms judged</td>
<td>- Diminished concentration/indecisiveness</td>
</tr>
<tr>
<td></td>
<td>to be due to</td>
<td></td>
</tr>
<tr>
<td></td>
<td>physical illness</td>
<td>- Weight loss/gain or a decrease in appetite</td>
</tr>
<tr>
<td></td>
<td>excluded</td>
<td></td>
</tr>
<tr>
<td>DSM-IV (inclusive)</td>
<td>All somatic</td>
<td>- Changes in sleeping pattern</td>
</tr>
<tr>
<td></td>
<td>symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>included</td>
<td>- Loss of energy</td>
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<tr>
<td></td>
<td>regardless of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>aetiology</td>
<td></td>
</tr>
<tr>
<td>Substitutive e.g. (Endicott, 1984)</td>
<td>Somatic</td>
<td>- Fearful or depressed appearance</td>
</tr>
<tr>
<td></td>
<td>symptoms are</td>
<td></td>
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<tr>
<td></td>
<td>substituted with</td>
<td>- Social withdrawal</td>
</tr>
<tr>
<td></td>
<td>additional</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cognitive-affective symptoms</td>
<td>- Brooding and self-pity</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cannot be cheered up</td>
</tr>
<tr>
<td>Exclusive e.g. (Cavanaugh, Clark, &amp; Gibbons, 1983)</td>
<td>Removal of somatic symptoms</td>
<td>- No somatic symptoms considered</td>
</tr>
</tbody>
</table>

If these criterion are actually more *bronze* than gold the question remains as to what is being compared with what? Until the diagnostic dilemma is satisfied efforts to pursue reliable screening methods for “depressive disorders” *may* be compromised. In response to this problem several schemas for depression diagnosis among physical illness have been devised, which are summarised in table 2.1. Although recent research has suggested the
utility of alternative criteria for diagnosis among physical illness (Akechi et al., 2009; von Ammon Cavanaugh, Furlanetto, Creech, & Powell, 2001; Whooley, Avins, Miranda, & Browner, 1997; Zimmerman, Chelminski, McGlinchey, & Young, 2006), the potential for false positive cases remains a concern (Koenig, George, Peterson, & Pieper, 1997), particularly as depression is a heterogeneous condition.

Some evidence suggests that the cognitive-affective symptoms of depression (guilt, loss of interest and low mood) are better discriminators of depression in ESRD patients than physical symptoms (Craven et al., 1987; Hinrichsen, Lieberman, Pollack, & Steinberg, 1989). Similarly, it has been suggested that depressed mood, morning depression and hopelessness are symptoms which differentiate depression in patients with physical illness (Hawton, Mayou, & Feldman, 1990). Using DSM-III criteria for major depression in ESRD patients, others suggest that depressed mood, anhedonia, feelings of guilt or worthlessness, slowed thought, and weight loss distinguished depressed and non-depressed patients, whereas loss of energy and sexual disinterest did not (Craven et al., 1987). Although such evidence generally supports the thesis that cognitive symptoms discriminate depression better than somatic symptoms, it is reported that somatic symptoms of depression do increase in severity as one nears the threshold for “caseness” (Clark, Cavanaugh, & Gibbons, 1983). Others suggest that somatic symptoms are useful discriminators (Moffic & Paykel, 1975), including data from a sample of HD patients (Drayer et al., 2006). Whether this is due to biased somatic reporting owing to increased negative affect is of course arguable.

While the best procedure for assessing depression among chronically ill populations remains contentious, it is still important to consider the possibility of depression when presented with physical symptomatology typical to mood disorders. Indeed in clinical practice an inclusive approach to depression assessment is advocated (Cohen-Cole, Brown, & McDaniel, 1993). After all, the pitfalls of false positive cases are far less than those of false negatives. Given current advances, the BDI has shown promise as a regular screening tool providing cut-off scores are adjusted (see chapter 4 and 5). The advantages of screening tools are that they can be used to assess larger populations, and monitor more easily depressive symptoms over time. Regular assessment may prove to benefit
psychosocial outcome among dialysis patients. However, the utility of regular depression screening was not supported in a systematic review of randomised control trials, in non-psychiatric settings (Gilbody, House, & Sheldon, 2001b). These data suggest that routine depression screening does little to improve psychosocial outcome, although interestingly depression recognition improved if screening questionnaires were administered by a non-clinician, with subsequent positive screens identified and then passed on to a clinician (Gilbody et al., 2001b). The heterogeneity of patients used may have influence the results, therefore the benefits of regular depression assessment among chronic populations requires further research.

2.3 Prevalence of depression and depressive symptoms in ESRD

The montage of research in the area suggests that depression accounts for around 50% of the psychopathology encountered in chronic physical illness. As in patients with ESRD the estimated prevalence of depression among patients with other physical illnesses is varied, and depends on the definition of depression employed and the type of depression measurement administered (Meakin, 1992; Rodin & Voshart, 1986). As a consequence, estimates of the prevalence of depression range between 15 and 61%, among the medically ill (Martucci et al., 1999). As stated previously, screening approaches generally inflate estimations compared to diagnostic assessments. For example, Smith et al (1985) compared three depression assessments among patient with ESRD, reporting varying prevalence rates across the assessments. When using the BDI (cut-off >11), 47% had significant symptomatology, compared to 17% when using the Multiple Affect Adjective Checklist and 5% after a professional diagnostic evaluation. In a recent study of ESRD patients treated with haemodialysis and peritoneal dialysis (n=128), 45.3% had a BDI≥14, while no differences between treatment modalities were apparent (Simic Ogrizovic et al., 2009).

Investigations employing diagnostic criteria among ESRD patients generally reveal lower estimates of depressive disorder, yet there is still variation across studies. A large epidemiology study reports that ESRD was associated with nearly a fourfold increase in depression prevalence as compared to healthy individuals (Egede, 2007). An early diagnostic study found that 8.1% of dialysis patients meet the DSM-III criteria for MDD.
(Craven et al., 1987), of which half had a history of depression. A recent investigation reports more than 70% of predominantly black ESRD patients had some form of psychopathology (Cukor et al., 2007). Among the 70 patients assessed with the SCID, 29% had a depressive disorder (20% Major depressive disorder, 9% dysthymia or other depressive disorder not specified). Moreover as is common in patients with ESRD, only 12% of the patients assessed were receiving treatment for depression or anxiety disorders (Cukor et al., 2007). Grant et al (2008) revealed a 12.3% prevalence rate after applying ICD-10 classification for depression to 57 HD patients. Others report a 17.3-19% prevalence of MDD in HD patients (Hedayati et al., 2006; Watnick et al., 2005). Analysis from the Dialysis Outcomes and Practice Patterns Study (DOPPS) cohort (n=6987) found a 13.9% prevalence rate of physician-diagnosed depression, compared to a 43% when using a CES-D cut-off of ≥10 (Lopes et al., 2004). Of the 12 DOPPS countries analysed, the USA had the greatest prevalence of physician diagnosed depression 21.7%. Variation in prevalence was not only evident across countries, but again dependent upon the assessment criteria. Italy had the highest prevalence of depression when using the CES-D≥10 (62.3%), yet only 15.5% had a physician diagnosis. Similarly, Japan had the lowest physician diagnosis of depression (2%), yet 40% had a CES-D≥10.

Empirical evidence demonstrates that the variation in prevalence is not only due to different methodologies employed in research, but also to population differences. In addition, studies based upon the DOPPS cohort suggest that some of the discrepancies between estimates obtained from diagnostic and self-report assessments may be due physician under diagnosis.

2.4 Prevalence of Depression in Chronic Kidney Disease

As described above there is considerable data concerning the estimated prevalence of depression in ESRD. However, in comparison there is a scarcity of research in CKD. Hedayati’s group in America have recently attended to this need by investigating the prevalence of Major Depressive Disorder (DSM-IV criteria), in patients with various stages of CKD (Hedayati, Minhajuddin, Toto, Morris, & Rush, 2009). Depression was found to be constant across CKD stages, with 21% of the sample meeting the criteria for MDD. This figure is indeed similar to estimates observed in ESRD. However, this data should be
appreciated with some caution as the sample consisted of mostly male veterans. Despite this limitation and the paucity of research in CKD, depression may be a prevalent psychopathology in early stages of kidney disease. This finding is pertinent as it has long been known that past depression predicts subsequent depression (Lewinsohn, Hoberman, & Rosenbaum, 1988). Indeed this has also been upheld in studies of depression in ESRD (Cukor et al., 2008; Sensky, 1989). The activation of depressogenic styles during CKD may be potent precursors of later depression, particularly after starting dialysis therapy, which is a significant stressor to the individual (c.f. Beck, 1967).

2.5 Dialysis initiation and depression symptoms

Data regarding depression symptoms following the initiation of dialysis therapy is limited (Korevaar et al., 2000). One if the first investigations to consider depression symptoms soon after dialysis initiation revealed that 45% of incident patients screened positive for depression on a three item measure derived from the diagnostic interview schedule (Walters, Hays, Spritzer, Fridman, & Carter, 2002). Similar findings were reported in a later study, with 44% of incident dialysis patients scoring ≥15 on the BDI (Watnick, Kirwin, Mahnensmith, & Concato, 2003). Of the depressed patients identified by Watnick et al only 16% were receiving treatment for depression. However it should be borne in mind that adjustment disorders and inadequate dialysis following the early weeks of dialysis may complicate the assessment of depression further.

There is a lack of data regarding the nature of dialysis initiation upon psychological functioning. Indeed, only one study to date has approached this problem in terms of depression symptoms (Miura, Kitagami, & Ohta, 1999). Miura et al (1999) assessed depression symptoms before and after dialysis initiation, comparing those with “ordinary introduction (OI)” with those who started as an emergency (emergent introduction- EI). The results indicated that both before and after dialysis introduction patients with an EI had greater depression symptoms as assessed by the Zung self-rating depression scale, as compared to those with an OI. While of interest it should be considered that this investigation suffered from a small sample size and lack of clinical data. In this instance the potential for confound maybe substantial.
2.6 The course of Depression in ESRD

A recent longitudinal study of HD patients, reports a 29% prevalence rate for depressive disorder using the SCID at baseline assessment (Cukor et al., 2008). Interestingly, 43% of patients diagnosed with depressive disorder at baseline, still satisfied the criteria 16 months later. A persistent depressive course was associated with reduced perceived health status and quality of life and a depressive history (Cukor et al., 2008). These results may imply that depression is relatively stable over time in ESRD patients, or that depression is not detected and treated adequately. Although this study had a relatively small sample size, it provides insight into the course of depression over time among HD patients. Other data suggest a trend for a decrease in depression symptoms in haemodialysis patients (House, 1987). In contrast a 3 year study of elderly dialysis patients found that around half had stable depressive symptoms, with around one-third worsening with time (Husebye, Westlie, Styrvok, & Kjellstrand, 1987). In peritoneal dialysis patients quality of life appears to decline over time (Bakewell, Higgins, & Edmunds, 2002), although this appears to be mostly due to decreased perceptions of physical function, rather than deteriorating mental health (Merkus et al., 1999; Mittal et al., 2001). Others have shown that mental health component scores of the SF-36 improved significantly over the first year of dialysis therapy (Korevaar et al., 2002). Given the paucity of longitudinal data specific to the assessment of depression symptoms, the trajectory of depression over stages of the dialysis career remains undefined.

2.7 The impact of depression in ESRD

The impact of depression upon health related outcome is tangible. In a recent study of HD patients, depression symptoms were associated with significantly more hospital admissions and emergency department visits (Tavallaii, Ebrahimnia, Shamspour, & Assari, 2009). In the general population depression is associated with increased mortality risk (Wulsin, Vaillant, & Wells, 1999), although methodological issues confound certain studies. A recent study investigated the impact of depression and anxiety symptoms using the Hospital Anxiety and Depression Scale (HADS) upon mortality in a large population survey (Mykletun et al., 2009). In a comprehensive analysis, the authors were able to demonstrate a significant effect of depressive symptoms upon survival after controlling for several factors including somatic conditions, physical activity and smoking status (OR=1.37, 95% CI 1.19 to 1.58).
Interestingly the adjustment of somatic conditions led to an attenuation of the depression-mortality association. Physical illness is therefore an important confound in this context, and suggests further the intimate relationship between depression and physical illness.

Cardiovascular disease (CVD) is a prominent co-morbidity among the dialysis population and one of the largest contributors of mortality (see chapter 1). There is also a comprehensive literature linking depression with CVD (Steptoe, 2007). Pro-inflammatory cytokines appear to be heightened in HD patients and predict mortality (Kimmel, Phillips et al., 1998). There is evidence that depression is associated with these cytokines including IL-6, IL-1β and TNF-α and CRP in both the general and ESRD populations (Appels, Bar, Bar, Bruggeman, & de Baets, 2000; Kop et al., 2002; Miller, Stetler, Carney, Freedland, & Banks, 2002; Simic Ogrizovic et al., 2009; Suarez, 2003). In a recent study, ESRD patients with a BDI≥14, had significantly higher IL-6 and hsCRP as compared to those with a BDI<14 (Simic Ogrizovic et al., 2009). Pro-inflammatory markers are associated in the pathogenesis of CVD (Ridker, Rifai, Rose, Buring, & Cook, 2002). It is proposed that immune functioning and inflammation mediates the link between depression and CVD (Lesperance, Frasure-Smith, Theroux, & Irwin, 2004). Efforts to investigate the complex pathways between depression, immune parameters and CVD in ESRD patients seem highly relevant particularly as CVD and depression remain prominent co-morbidities among HD patients. In addition, research has shown associations between depressive affect and malnutrition in ESRD patients (Koo et al., 2003), although the related causality remains unknown. There is evidence of the association between malnutrition, inflammation, and atherosclerosis (MIA) in ESRD patients (Honda et al., 2006; Wang et al., 2004); some have suggested that depression could be involved in MIA syndrome (Simic Ogrizovic et al., 2009), albeit with a great need for further investigation.

Although detailed description of the behavioural and pathological mechanisms underlying depression and mortality is beyond the scope of this chapter, there is evidence linking depression and mortality among the ESRD population (Boulware et al., 2006; Drayer et al., 2006; Einwohner, Bernardini, Fried, & Piraino, 2004; Hedayati et al., 2008; Kimmel et al., 2000; Lopes et al., 2004; Lopes et al., 2002; Shulman, Price, & Spinelli, 1989), including those withdrawing from dialysis (Lopes et al., 2004; McDade-Montez, Christensen,
Cvengros, & Lawton, 2006). A summary of this literature is presented in table 2.2. It should be noted that while a depression-mortality association is well established, the association between depression and withdrawal may be confounded by the fact that depression symptoms are likely to increase the nearer to death. Depressive symptoms (BDI≥11) have also been found to predicted peritonitis in a study of 162 PD patients after controlling for age, diabetes, race and coronary artery disease (hazard ratio= 2.7, 95% CI 1.23 and 6.03). However whether this was due to diminished health care behaviour or impaired immunological function is not known (Troldle et al., 2003). Furthermore given the current evidence regarding suitable BDI cut-off scores in ESRD, a BDI ≥11 may be considered too low as these scores requirement adjust in this patient group (Grant et al., 2008).

It is important to note, that while most outcome studies control for co-variates such as co-morbidity and age, studies differ with regards to the measurement of depression (symptom severity vs. diagnostic) and analytic techniques (time varying models, vs. fixed baseline models). Indeed, some studies have reported null findings with regards to any association between depression and mortality in ESRD patients (Christensen, Wiebe, Smith, & Turner, 1994; Devins et al., 1990). Kimmel et al (2000) investigated the association between depression and mortality in 295 HD patients using the BDI and CDI. In adjusted models baseline depression scores failed to predict mortality. However in time-varying models, both the BDI and CDI predicted mortality after controlling for a range of clinical parameters (table 2.2). Bowlware et al (2006) investigated the relationship between depressive symptoms, cardiovascular events and mortality. Time varying models demonstrated that symptoms of depression were associated with increased all cause mortality and cardiovascular events at a 2 year follow-up, whereas baseline measures did not. This association was attenuated, however, after a 6-month time lag was incorporated into the analysis. This suggests that deteriorating co-morbidity may at least partially explain the association between depression and mortality rather than depression worsening morbidity. Both Kimmel et al (2000) and Boulware et al (2006) employed depression screening tools to assess depressive symptoms. In the case of the latter study, depression was assessed using a non-conventional approach (subscale from the Medical Outcomes Study Short Form-36 questionnaire).
Recently the association between a formal diagnosis of clinical depression and mortality has been established (Hedayati et al., 2008). Ninety eight HD patients were assessed using the SCID, which identified 26 as suffering from depressive disorder. Differences between the depressed (as diagnosed via the SCID) and non-depressed revealed a greater prevalence of co-morbidity in the depressed. In multivariate analysis after controlling for age, ethnicity, gender, time of dialysis and co-morbidity, a diagnosis of depression was significantly associated with mortality. Interestingly, self-report measures were not significant predictors of mortality in sub-analysis.

In summary there is considerable evidence regarding the association between depression and mortality in ESRD patients. While further research is required to better understand this relationship, it is also important to establish the utility of treating depression upon patient outcome of which the current evidence is mixed (Detweiler-Bedell, Friedman, Leventhal, Miller, & Leventhal, 2008).

2.8 Depression and Non-Adherence

Depression may be associated with increased health care costs and mortality due to decreased treatment adherence in these patients (DiMatteo, Lepper, & Croghan, 2000). A meta-analysis of depression and medical treatment non-adherence suggests that depression increases the odds of non-adherence 3 fold (odds ratio 3.3, 95%CI 1.96 to 4.89, DiMatteo et al., 2000). Interestingly analysis of six ESRD studies were reported in this meta-analysis, revealing a standardised odds ratio of 3.44 (95% CI 1.26-8.1, p=0.008) for non-adherence in depressed patients. Critically however, this analysis did not weight the effect size for methodological strengths for each study reported. A recent review of the literature evaluated the association between depression and non-adherence more cautiously (Raynor, Wing, & Phelan, 2006). Indeed, while 37% of the studies reviewed (n=41), report a significant negative association, a similar number reported that depression was related to some aspects of non-adherent behaviour but not all. These findings highlight the complexity of adherence and show that predictors may only partially explain one aspect of what are often demanding and multifaceted treatment regimes. Furthermore measuring adherence in the ESRD is a particular issue due to several clinical confounders (Leggat et al., 1998). Kimmel et al (1998) suggest investigating behavioural non-adherence relating to the
dialysis treatment (i.e. shortening dialysis time and skipping dialysis sessions). They demonstrated that depression symptoms were associated with behavioural non-adherence, and that non-adherence predicted mortality. However in this particular analysis they failed to find any association between depression symptoms and mortality.

Recently the influence of depressive symptoms upon medication adherence in both ESRD and kidney transplantation patients has been investigated (Cukor, Rosenthal, Jindal, Brown, & Kimmel, 2009). The results showed that depressive symptomatology added significantly to the explained variation of medication adherence in both ESRD and transplant patients. Given this, it may be hypothesised that treating depression in ESRD patients would improve patient adherence. Some evidence suggests that treating depression improves dietary adherence in non-insulin dependent diabetics (Goodnick, Kumar, Henry, Buki, & Goldberg, 1997). However other studies report mixed findings in this regard (Lustman, Griffith, Freedland, Kissel, & Clouse, 1998), and several methodological concerns confound certain studies. Prospective cohort studies are therefore required to test this hypothesis in ESRD patients.

2.9 Clinical associations of depression

The aetiology of depression in ESRD is probably complex and multifaceted. As already discussed, depression is associated with elevated inflammatory cytokine levels, suggesting that inflammatory processes have a possible role in the aetiology of depression. This is postulated to occur as a result of cytokine stimulation of the hypothalamic-pituitary-adrenal axis, affecting serotonin, its precursor tryptophan and noradrenergic systems that are implicated in the pathogenesis of depression (Barden, 2004; Wichers & Maes, 2002). However the causal relationship between depression and inflammation is indeed complex and not well delineated. Results from a recent longitudinal study conducted in a sample of healthy 50-70 year olds, suggests that depressive symptoms precedes changes in IL-6 (Stewart, Rand, Muldoon, & Kamarck, 2009). It is clear that further investigations are required to increase our understanding of the depression-inflammation relationship, particular with reference to dialysis patients of whom inflammatory responses are common.
Among the ESRD literature, there is preliminary evidence that depression is associated with increased immune-activity (Simic Ogrizovic et al., 2009). However others have found no association between depressive symptoms and proinflammatory cytokines in ESRD patients (Dervisoglu, Kir, Kalender, Eraldemir, & Caglayan, 2008). For example, among patients on HD, PD and conservative management, Dervisoglu et al (2008) found no association between IL-6 and TNF-α cytokine levels and depression (defined as a BDI ≥17). Similarly the BDI failed to correlate with these indices (Dervisoglu et al., 2008). While depression and inflammation may serve as adaptive evolutionary mechanisms in response to illness, their relationships in ESRD may be complicated as chronic inflammatory states are common in this population. Whether such states are related to depression is not yet understood.

Previously it was reported that uraemia itself may, possibly via an effect on the synthesis and metabolism of certain neurotransmitters, cause depression and suggested a possible genetic predisposition within the ESRD population (Israel, 1986; Smogorzewski, Ni, & Massry, 1995). Daily dialysis has been shown improve the quality of life in observational studies (Vos et al., 2006); a reduction in uraemic symptoms may improve depressive symptomatology (Heidenheim, Muirhead, Moist, & Lindsay, 2003; Kooistra, Vos, Koomans, & Vos, 1998). We await with interest the full results from the FREEDOM study, in which clinical and psychosocial parameters are included in the comparison of haemodialysis patients on daily HD with a matched group on thrice-weekly HD (Jaber et al., 2009).

Analysis of the DOPPS cohort found that white race, age, female sex and greater dialysis vintage was associated with depression (Lopes et al., 2002). In addition depression has been associated with co-morbidities in ESRD including coronary heart disease and diabetes (Hedayati et al., 2006; Hedayati et al., 2005; Lopes et al., 2002), although there are inconsistencies in the literature. However the actual correspondence between reported symptoms and physical states can be inaccurate (Pennebaker, 1982), suggesting that the interpretation of illness and its severity, rather than co-morbidity per se, is a greater determinate of affect (Sacks et al., 1990). Indeed, evidence in other patient groups has generally failed to find direct relationships between disease severity (morbidity) and the extent of depression (Peck, Smith, Ward, & Milano, 1989).
Others have investigated possible dialysis-specific associations with affect. For example, the use of polysulfone dialysers in relation to depression was the focus of a recent investigation (Hsu, Chen, & Wu, 2009). The rationale was that polysulfone dialysers reduce inflammation during dialysis (Walker, Sutherland, & De Jong, 2004). The authors compared HD patients using polysulfone dialysers with cellulose derivative dialysers, with regards to depression symptoms using the Hospital Anxiety Depression Scale (HADS). A HADS depression score of >8 was used to define significant depressive symptoms. The results demonstrated that polysulfone dialysers reduced the odds of depression in multivariate analysis. However, the depressed and non-depressed groups did not differ in their inflammatory or malnutrition markers, making the basis for this finding uncertain. These results are probably confounded by the small sample and significant selection bias with regards to which patients used polysulfone dialysers. Larger controlled studies, looking at the biocompatibility of dialysers in relation to depressive symptoms, would nevertheless be of interest.

Restless leg syndrome (RLS) is more prevalent in ESRD than in the general population, and is associated with insomnia, mortality and depression (Montplaisir et al., 1997; Sevim et al., 2004; Takaki et al., 2003; Unruh et al., 2004). In a large cohort of transplant and dialysis patients, RLS was predictive of significant depressive symptoms (CES-D >18) after controlling for several covariates including albumin and the number of co-morbidities (Szentkiralyi et al., 2009). Interestingly this association was independent of insomnia, suggesting that a lack of sleep did not mediate the relationship between RLS and depression (Szentkiralyi et al., 2009). When the dialysis patients were analysed separately, an even stronger association was observed. Pain, fatigue and helplessness are some of the potential mediating factors put forward to explain the association between depression and RLS (Kushida et al., 2007; Ulfberg, Nystrom, Carter, & Edling, 2001). However, causality cannot be inferred here, as it is also possible that depressive behaviours (e.g. lack of exercise,) may lead to RLS (Aukerman et al., 2006).
Table 2.2: The association between depression and outcome in ESRD patients

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Assessment</th>
<th>Model</th>
<th>Outcome</th>
<th>Adjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Boulware et al., 2006)</td>
<td>917</td>
<td>MHI-5 (≤52)</td>
<td>Baseline</td>
<td>All deaths</td>
<td>1.24 (0.81 to 1.89)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CVD deaths</td>
<td>0.72 (0.30 to 1.73)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Time Dependent</td>
<td>All deaths</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CVD deaths</td>
<td>3.27 (1.57 to 6.81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Six to month lag</td>
<td>All deaths</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CVD deaths</td>
<td>0.89 (0.28 to 2.83)</td>
</tr>
<tr>
<td>(Kimmel et al., 2000)</td>
<td>295</td>
<td>BDI</td>
<td>Time varying</td>
<td>All deaths</td>
<td>1.32 (1.13 to 1.55)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CVD deaths</td>
<td>1.23 (1.05 to 1.43)</td>
</tr>
<tr>
<td>(Einwohner et al., 2004)</td>
<td>66</td>
<td>Zung SDS</td>
<td>Baseline</td>
<td>All deaths</td>
<td>1.05 (1.01 to 1.08)</td>
</tr>
<tr>
<td>(Lopes et al., 2002)</td>
<td>5256</td>
<td>Physician Diagnosis</td>
<td>Baseline</td>
<td>All deaths</td>
<td>1.23 (1.08 to 1.40)</td>
</tr>
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<td></td>
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<td></td>
<td>1st Hospitalisation</td>
<td>1.11 (1.01 to 1.22)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>“down in the dumps”</td>
<td>All deaths</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1st Hospitalisation</td>
<td>1.15 (1.04 to 1.27)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>“down hearted and blue”</td>
<td>All deaths</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1st Hospitalisation</td>
<td>1.11 (1.01 to 1.22)</td>
</tr>
<tr>
<td>Study</td>
<td>n</td>
<td>Assessment</td>
<td>Model</td>
<td>Outcome</td>
<td>Adjusted Relative Risk (95% CI)</td>
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<tr>
<td>(Lopes et al., 2004)</td>
<td>6987</td>
<td>CES-D ≥10</td>
<td>Baseline</td>
<td>All deaths</td>
<td>1.42 (1.29 to 1.57)</td>
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<td></td>
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<td></td>
<td>1st Hospitalisation</td>
<td>1.12 (1.03 to 1.22)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Withdrawal</td>
<td>1.55 (1.29 to 1.85)</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Physician Diagnosis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All deaths</td>
<td>1.26 (1.10 to 1.43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1st Hospitalisation</td>
<td>0.97 (0.86 to 1.09)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Withdrawal</td>
<td>1.42 (1.11 to 1.80)</td>
</tr>
<tr>
<td>(Hedayati et al., 2008)</td>
<td>98</td>
<td>SCID</td>
<td>Baseline</td>
<td>Death/hospitalisation</td>
<td>2.07 (1.10 to 3.90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BDI</td>
<td></td>
<td></td>
<td>1.01 (0.96 to 1.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDI</td>
<td></td>
<td></td>
<td>0.99 (0.94 to 1.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CES-D</td>
<td></td>
<td></td>
<td>1.01 (0.98 to 1.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BDI ≥14</td>
<td></td>
<td></td>
<td>0.86 (0.45 to 1.64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CES-D ≥18</td>
<td></td>
<td></td>
<td>1.06 (0.58 to 1.96)</td>
</tr>
<tr>
<td>(Drayer et al., 2006)</td>
<td>62</td>
<td>PRIME-MD</td>
<td>Baseline</td>
<td>All deaths</td>
<td>4.1 (1.2 to 13.8)</td>
</tr>
<tr>
<td>(McDade-Montez et al., 2006)</td>
<td>240</td>
<td>CDI</td>
<td>Baseline</td>
<td>Withdrawal</td>
<td>1.06^a p&lt;0.05^b</td>
</tr>
<tr>
<td>(Riezebos, Nauta, Honig, Dekker, &amp; Siegert, 2010)</td>
<td>101</td>
<td>HADS-D ≥7</td>
<td>Baseline</td>
<td>Mortality</td>
<td>11.7 (1.6 to 82)</td>
</tr>
</tbody>
</table>

^aAdjusted Hazard Ratio ^bno CI described. Zung SDS: Zung Self-report Depression Scale. BDI: Beck Depression Inventory. CDI: Cognitive Depression Index. PRIME-MD: Primary Care Evaluation of Mental Disorders Mood Module. CES-D: Center for Epidemiologic Studies Depression Scale. MHI-5: 5 item subscale from the Medical Outcomes Study Short Form-36. “down in the dumps” and “down hearted and blue”: items from the Kidney Disease and Quality of Life Short Form. ^80 HD and 21 PD patients
2.10 Associated psychological features of depression in ESRD

A number of studies have focused upon the psychological factors associated with depression in ESRD, with particular reference to internal locus of control (Baydogan & Dag, 2008; Christensen, Turner, Smith, Holman, & Gregory, 1991). Earlier work from the Lister hospital observed a negative association between internal health locus of control and depression symptoms (Chilcot, Farrington, Wellsted, & Da Silva-Gane, 2008). Other work has shown the importance of perceptions of control and feelings of helplessness in the onset and maintenance of depression in ESRD patients, for example feelings of uncontrollability and perceptions of illness intrusiveness (Christensen & Ehlers, 2002; Devins, Binik, Hollomby, Barre, & Guttmann, 1981; Devins et al., 1983). The concept of loss received attention in a recent study among 151 ESRD patients (Chan, Brooks, Erlich, Chow, & Suranyi, 2009). Perceptions of loss were the strongest predictors of depression, which in turn predicted quality of life. Likewise, loss may be closely associated with perceptions of helplessness and uncontrollability.

It has been suggested that perceptions of control and mastery are significant factors involved with cognitive adaptation to illness (Taylor, 1983). One study reports that a high illness identity (a self-concept congruent with a stereotypical kidney patient) correlated with illness intrusiveness and emotional distress (Devins, Beanlands, Mandin, & Paul, 1997). The authors propose that in individuals whose self concept is “tied” to that of illness, perceive less non-illness rewards and experiences thus predisposing them to depression.

More recent work has focused upon underlying illness schema in predicting depressive symptoms among ESRD patients (Guzman & Nicassio, 2003). Self-schema refers to cognitive generalizations that impact upon the selection and processing of self relevant information (Markus, 1977). Having a negative illness schema would lead to biased processing with regards to negative health related information, that would typically lead to negative appraisals and perceptions. Guzman et al (2003) found in 109 ESRD patients that negative illness schemas were associated with higher BDI and CDI scores, whereas positive illness schemas were associated with reduced depression scores. Although this study suffers with some methodological concerns, including its cross sectional design, negative cognitions
(and underlying schemas) may be important determinants of depression in ESRD patients. Attempts to reconfigure such negative beliefs by psychological intervention seem highly relevant. In support of this line of research some work in ESRD has shown the importance of illness appraisals upon mood independent of disease severity (Sacks et al., 1990), while other studies have revealed associations between illness representations and quality of life among ESRD patients (Covic, Seica, Gusbeth-Tatomir, Gavrilovici, & Goldsmith, 2004; Griva, Jayasena, Davenport, Harrison, & Newman, 2009; Timmers et al., 2008). The association between illness perception and depression receives further attention in the following chapter.

### 2.11 Treatment options for depression in ESRD

Among patients with ESRD there are several treatment options available, all of which should be accompanied by supportive, educational and problem-solving strategies (MacHale, 2002). A systematic review of antidepressants in patients with a physical illness provides evidence for the effectiveness of drug treatment compared to no-treatment or placebos (Gill & Hatcher, 1999). The authors reported that 4.2 patients need to be treated to produce one recovery (95% CI: 3.2 - 6.4) although this is somewhat crude as it does ignore improvements in affect.

Data from the DOPPS cohort revealed that among ESRD patients with a physician diagnosis of depression, only 34.9% were on antidepressants (Lopes et al., 2004), although the rate in Japan is reported to be only 1.2% (Fukuhara et al., 2006). Although this does not include the number of patients receiving psychotherapy, it appears that many patients are not receiving adequate treatment for their depressive disorders. It is thought that even fewer patients are receiving antidepressant medication at the start of dialysis therapy, a time when the onset of depression may be more frequent (Watnick et al., 2003). As previously stated, depression or adjustment disorders may manifest during this time period, thus suitable recognition and treatment would appear to be important.

In ESRD the prescription of antidepressants requires some caution as there is potential for drug-drug interactions. The general guidance for anti-depressant prescription in this setting is to start at a lower dose and increase gradually (Kennedy, Craven, & Rodin, 1989;
MacHale, 2002). Generally older tricyclic medications have an adverse cardiac profile, thus merit caution in ESRD patients. Selective serotonin reuptake inhibitors (SSRIs) have more favourable side effect profiles, although they may increase some uraemic symptoms. Several small investigations have demonstrated the effectiveness of SSRI’s in dialysis patients (Blumenfield et al., 1997; Levy et al., 1996). As a part of an 8 week trial, Levy et al (1996) gave both depressed renal and depressed non-renal patients, 20mg/d of fluoxetine. In both patient groups, depressive symptoms were reduced significantly in 5 of the 6 patients. The authors reported no adverse effects in the renal group (Levy et al., 1996). The results also indicated that there were no pharmacokinetic difference between HD and non-renal patients, as both groups had similar plasma concentrations of fluoxetine (and norfluoxetine). Similarly fluoxetine (20mg daily), in a double blind placebo controlled study of HD patients, was effective in alleviating depression symptoms with no significant side effects (Blumenfield et al., 1997). Citalpram is thought to be safe considering its similarly with fluoxetine (Cohen, Tessier, Germain, & Levy, 2004). It is suggested however that fluoxetine should be avoided in diabetics due to its potential to change serum glucose levels. Furthermore duloxetine (Cymbalta), a serotonin-norepinephrine reuptake inhibitor, is not recommended for use in patients with ESRD (Preskorn, 2004).

A wider issue concerns the fact that some patients refuse treatment, while other are non-adherent to antidepressants medication (Wuerth et al., 2001). One recent study suggests that patients may be unaware of depressive or anxiety symptoms, or feel that they do not require attention (Johnson & Dwyer, 2008). Understanding the possible barriers raised by these issues is of importance if patients are to receive suitable treatment for depression.

The possible side effects and drug -drug interactions presented by psychotropic intervention highlight the need to establish and implement effective psychological interventions in patients with ESRD. Used solely or in parallel with drug treatment, psychological therapy has been used widely across a range of chronic illnesses. Of these, cognitive behavioural therapy (CBT) has been shown to be effective (Cukor, 2007; Cukor & Friedman, 2005; Lustman et al., 1998; White, 2001). A recent trial of group CBT was found to be an effective treatment for depression in HD patients (Duarte, Miyazaki, Blay, & Sesso, 2009). Forty-one patients underwent a 12 week group CBT intervention, in comparison to
44 control patients whom received standard care. At both 3 and 9 months follow up, the intervention group scored significantly lower on the BDI, and on items of the Mini International Neuropsychiatric Interview (M.I.N.I). This study, despite a few limitations, highlights the promise of CBT as a treatment option for dialysis patients. Further, a recent randomized, controlled, pilot investigation used CBT as an intervention to improve sleep quality in peritoneal dialysis patients and found it to be effective. Although several confounding factors may have influenced the results, this evidence adds to the potential benefit of CBT in improving quality of life among ESRD patients. Despite these advances there is a great need for further studies investigating the treatment options available for depressed ESRD patients.

The empirical works presented here investigate the association between depression and illness representations in ESRD. As reviewed in the following chapter, maladaptive illness cognitions are associated with various health related outcomes, including depression and reduced quality of life. Therefore a prerequisite to further interventional research in ESRD is to understand the nature and content of patient’s illness cognitions in relation to affect.

2.12 Concluding Remarks
This chapter provided a review of depression in ESRD. The issues encountered when assessing mood in individuals with a chronic illness were discussed, but will be considered further in chapter 4. These issues are highly relevant in ESRD, due to the nature of renal failure and its symptoms. Although there is no consensus as to how to assess depression in this setting, evidence suggests that 20-30% of patients experience significant depressive symptoms. While the evidence in the ESRD population is complex, it is sufficient to link depression with adverse outcomes. Given this, it is alarming that depression is under recognised and under treated. It is therefore necessary to identify antecedent factors that are amenable to intervention. Indeed, there is a vast need to establish viable treatments for ESRD patient. CBT may be an important therapeutic method although further trials of psychotropic and psychotherapeutic interventions are required.

The psychological and clinical parameters associated with depression are becoming evident, although a vast amount of research is still required if we are to understand the
pathogenesis of depression in ESRD. The aim of this thesis is to increase this level of understanding, by applying the self-regulatory illness representation model to the understanding of depression in ESRD. The following chapter outlines this model, describes its development, and presents empirical data for the utility of the self-regulatory model of illness representations in the context of physical illness.
Chapter 3

Self-Regulation in Heath and Illness: The Common Sense Model of Illness Representations

- “Health is not valued till sickness comes”

Thomas Fuller (1608-1661)

3.1 Introduction

The aetiology of depression is conceptualised as a diathesis-stress model in cognitive theory (Beck, 1967). Therefore like other co-morbidities in ESRD, individuals have psychological risk factors (diathesis) which become activated by environmental or internal stressors. The onset of illness may be an important stressor that activates the depressive vulnerability, defined as depressive schema in cognitive theory (Beck, 1967). The interpretation and self-regulation of the illness event (i.e. the potential stressor) is potentially critical, as according to the principles of cognitive theory, the matching of the input stimulus with underlying depressive schema leads to depression. With this context the interpretation of illness may be important determinants of affect. It has been proposed that the interpretation and adaption to illness is best defined in terms of self-regulatory processes, with particular emphasis on the Common-Sense Model (CSM) of Illness representations. Although the entirety of the CSM model is not examined in this thesis, the present chapter aims to set the landscape and rationale behind studying illness representations in ESRD. The content of this chapter is organised as follows: 1) a concise overview of self-regulation and the historical development of CSM, 2) a description of the fundamental tenets of the CSM, 3) a review of empirical support for the CSM and of the model’s utility as applied psychological and clinical outcomes in chronic physical illnesses, and 4) a review of research into illness representations in ESRD. The reviews have drawn on searches of the Pubmed, Psycinfo, and the Web of Knowledge databases.

Self-regulation is inherent to being human; it is the ability to set goals and adapt one’s behaviour in order to attain them (Scheier & Carver, 2003). This involves exerting control over internals states and responses (Baumeister, Heatherton, & Tice, 1994). In other words, humans strive to attain standards or goals by altering their thoughts, desires, emotions and
behaviours (Carver & Scheier, 1998). Moreover, it has been suggested that any system capable of problem solving has the potential to self-regulate (Powers, 1973). A generic conceptualisation is seen in cybernetic control theory (Miller, Galanter, & Pribram, 1960), which is governed by the TOTE framework (test, operate, test, and exit). According to TOTE, a self-regulatory system first tests an input against a standard (reference value). It then operates a procedure to reduce or in some instances increase the discrepancy between the input and reference value. The system then undergoes a further test against the reference value. This process is repeated until concordance is achieved between the input and reference value, at which point the process is ended (exit). The basic feedback architecture of TOTE underpins general models of self-regulation (Carver & Scheier, 1981), in which goals serve as reference values from which one’s current state (input function) is evaluated. Discrepancy between the goal standard and the input function, leads to the implementation of strategies to achieve the goals, which are then appraised as to their success at moving closer to the goal state (Carver & Scheier, 1981).

While an in-depth account of self-regulation as applied to human behaviour is beyond the scope of this chapter, the description provided above represent key features of a self-regulatory process, which also apply to the understanding of human behaviour and adaption. The discussion presented in this chapter will be constrained to self-regulation pertaining to health and illness, to which the work of Howard Leventhal and colleagues has been seminal. The Common Sense Model (CSM) specifically addresses self-regulatory processes encountered during the prevention, adaption and maintenance of behaviours relating to the disease (Leventhal et al., 1980; Leventhal et al., 1984). The CSM departs from social-cognitive models of health behaviour including the Theory of Planned Behaviour (Ajzen, 1991) and the Health Belief Model (Rosenstock, 1974). Although all infer that perceptions (or attitudes) from a part of the basis for motivated behaviour, the CSM describes these representations as both concrete experiential and abstract schematic components (Leventhal, Diefenbach, & Leventhal, 1992; Leventhal, Leventhal, & Contrada, 1998). Moreover, the CSM defines at least five illness perceptions that coalesce to form an illness representation which operates within an individual’s pre-existing cognitive schema of illness.
The CSM posit that individuals are active problem solvers motivated to resolve the threat of illness (Leventhal et al., 2003). The targets (goals) that are being strived towards, refer to the somatic experiences, emotions, and competencies that evoke from the “physical and psychological self” (Leventhal et al., 2003). The strategies or procedures undertaken for regulation (i.e. health behaviours, emotional regulation) are the result of the interpretation of the health threat (i.e. the illness representation), and the emotional reaction to the threat. Therefore unlike general models of self-regulation (Carver & Scheier, 1981), the CSM not only defines the self regulatory process, but also provides content as to what is being regulated (Leventhal et al., 2003). This content refers to illness representations, or cognitions, that define the problem and set procedures for dealing with the illness threat.

The work to be presented in this thesis argues that illness representations predict depression in ESRD, and both depression and illness representations are associated with adverse outcomes. However it should be noted that illness representations are more than just perceptions of illness. They sit within a specified content driven model of self-regulation pertaining to health and illness (CSM). Therefore, the terms illness representations and illness perception are used interchangeably throughout this thesis depending upon the context in which they are described. Illness representations refer to the mental models of illness individuals hold, whereas the term illness perception is used to refer to single cognitions pertaining to a facet of the disease, for example how long will it last, or can it be controlled? An elaboration of the CSM and its development is provided in the following section.

3.2. Historical Development of the CSM: the parallel response model

The CSM is an extension of the parallel response model which arose from studies investigating fear communication (Leventhal, 1970). Early work on fear communication was influenced by the Fear-Drive Model (Dollard & Miller, 1950), which stated that fear was a motivation state, and that behaviours or procedures that reduced fear would be reinforced or learnt via Pavlovian and Instrumental conditioning. Leventhal and colleagues undertook a series of experiments designed to test the assumptions of the Fear-Drive Model. These experiments evaluated the compliance to recommended health behaviour following the communication of either high or low fear messages. In multi-factorial designs, fear
messages were combined with other factors including *action planning*. The hypothesis according to the fear-drive model was that *high fear* would produce the *uptake* of recommended health behaviour if paired with a procedure that reduced the motivational fear state. Data from numerous experiments (Dabbs & Leventhal, 1966; Leventhal, Singer, & Jones, 1965; Leventhal & Watts, 1966) found that high-fear messages were more effective in producing *attitudinal* change towards a behaviour (i.e. taking a tetanus shot and smoking cessation), compared to low-fear messages, although the effect was time limited generally disappearing between 24 -48 hours (Leventhal, 1970; Leventhal & Niles, 1965). Moreover, two consistent findings discredited the models assumptions; 1) high fear messages were no more influential at producing *actual* health care behaviour as compared to low fear messages, and 2) either *high or low* fear messages *paired* with procedures for action (i.e. action plan) elicited overt health care behaviours (Leventhal, 1970). To illustrate, student participants were more likely to attend a clinic to receive tetanus if a fear message was presented to the participants accompanied by a plan of action, which in this instance was to examine their daily schedule and plan a time when they would be near to the university clinic (Leventhal et al., 1965). Although there was no apparent interaction between fear state (high vs. low) and the presence of action plans upon overt behaviour, it was clear that fear was a *required* state as action plans alone failed to elicit behaviour (Leventhal, 1970; Leventhal & Niles, 1965). Put another way, explicit plans regarding a health behaviour including when, how, and where to do it, was a poor predictor of actual behaviour in the absence of fear. These results led to the development of the parallel response model (Leventhal, 1970). This model posits two parallel responses to illness threats; an emotional state (fear control) which leads to the development and implementation of procedures to control the fear, as well as a *cognitive representation* of the threat and a need for corresponding procedures to control the threat (danger control, see figure 3.1). Therefore following an illness threat, parallel emotional and cognitive systems serve as the interpretive stage of the self-regulatory process, guiding the selection and implementation of coping procedures, which are then appraised as to their efficacy. The appraisal represents the feedback process in which the outcome of the coping procedure is compared with the goal standards. Discrepancy between the input and goal standards (i.e. in TOTE) leads to continued self-regulation.
3.3. A description of the CSM

3.3.1 The bi-level nature of illness representations

While it was clear from studies into fear communication that fear per se was not the essential motivation for the uptake of health care behaviour, the question remained; was there anything inherent to the threat message and its interpretation that influenced how individuals react and cope to the threat? A series of experiments were undertaken to address this question which involved studying patients about to undergo noxious medical procedures (Johnson, 1975; Johnson & Leventhal, 1974). For example during an endoscopy, the somatic sensations perceived during the procedure can elicit avoidance reactions if they are interpreted as signs of danger. Johnson and Leventhal (1974) conducted a study which varied two factors before an endoscopy examination, 1) sensory information and 2) specific coping instructions. Patients who were prepared with concrete information about the somatic sensations associated with endoscopy, where the sensations were identified as non-threatening, and action plans described for dealing with these sensations (breathing technique), gagged less during the procedure as compared to control patients who received standard care. Patients who monitored these somatic sensations could reduce or even eliminate fear because they were guided by a perceptual representation of the experience, which directed problem focused coping procedures in order to effectively self-regulate. This data suggests that the motivation effects behind a given heath behaviour is driven by efforts to control danger (cognitive representations) and fear (emotion), which are influenced by patient’s concrete perceptual experience and their interpretation. Moreover,
this data suggested that health threats were bi-level, represented as abstract linguistic (semantic) codes, and as concrete perceptual experiences. Further research revealed that this bi-level feature not only pertained to the experience of emotion, but also to the identity of the illness. For example in a study of patients undergoing treatment for hypertension, 90% reported they could tell when their blood pressure was up due to perceived symptoms like flushed faces and headaches (Meyer, Leventhal, & Gutmann, 1985). Moreover, hypertensive patients were more adherent to medication if they believed that their medication controlled their symptoms (Meyer et al., 1985). However, 80% of the same sample reported, “people cannot tell when their blood pressure is up.” This data suggests that hypertensive patients held a bi-level representation of their condition; one that was based upon their concrete experience (i.e. my flushed face indicates a rise in my blood pressure), and the other based upon abstract semantic knowledge (that hypertension is asymptomatic). Others have produced complementary data showing that symptoms and illness labels are cardinal to illness representations in conditions such as cancer (Nerenz, Leventhal, & Love, 1982) and even in common illnesses such as colds (Lau & Hartman, 1983). Taken together it appears that illness representation are complex multi-level concepts that can influence the interpretation, reporting and behaviours surround illness.

3.3.2 Interactions between abstract and concrete illness representations: The Symmetry Rule

Hypertension studies and studies of fear communication had found that illness representations were bi-level for both their emotional and cognitive components. Moreover there appeared to be a linkage between the concrete perceptual and abstract semantic representations. Indeed it was apparent that there was pressure or a heuristic to connect the concrete and abstract levels of representation (Meyer et al., 1985). This pressure termed symmetry rule, refers to the need to find an illness label (illness identity) given the experience of symptoms, and the need to identify symptoms once given a label. This notion compares with the theory of cognitive labelling of emotion, which posits that physiological arousal promotes a search for a label based upon the cognitions available to the individual (Schachter & Singer, 1962). The perception of arousal or change in internal states rather than actual change, has also been shown to be sufficient to start the cognitive
labelling process (Ross, Rodin, & Zimbardo, 1969). That is, the experience of arousal starts the search for an attribution of label to explain the arousal state.

The influence of these two levels of representation (abstract and concrete) upon fear was the focus of subsequent research. Easterling and Leventhal (1989) report that women who perceived themselves as vulnerable to breast cancer, reported increase worry (fear) with an increase in perceived physical symptoms, despite the fact that the symptoms reported were not cancer specific. Therefore the interaction of physical symptoms (concrete representation) and an illness identity (vulnerability-abstract representation) lead to increased fear about potential cancer risk. Indeed, it was apparent that both symptoms and vulnerability were required to generate fear as either alone failed to increase worry (Easterling & Leventhal, 1989). This data suggest that the linkage of abstract and concrete representations provided a coherent representation, which in this instance increased illness-related worry with regards to cancer risk.

Studies of hypertension provided further support for the symmetry rule. Meyer et al (1985) found that patients new to treatment were likely to report that their condition was symptomatic the longer they were in treatment. An illness label drove the selective search for “common-sense” symptoms based upon underlying illness schema. This data was confirmed in laboratory conditions. Students who were provided false-feedback as to their blood pressure reading (e.g. high blood pressure) reported experiencing a greater number of symptoms such as headaches and flushed faces (Baumann, Cameron, Zimmerman, & Leventhal, 1989). Furthermore, this data supports the work of Pennebaker (1982) and Pennebaker and Skelton (1981) which demonstrated that cognitive schema influence the selection and reporting of somatic sensations. In one study, participants were told that the effects of an ultrasonic noise (bogus) upon task performance was being investigated (Pennebaker, 1982; Pennebaker & Skelton, 1981). The participants were led to believe that the ultrasonic noise may lead to either increases or decreases in skin temperature. A control group were told that skin temperature would be monitored but received no information regarding ultrasonic noise effects. After the schema manipulation, a thermister was attached to participant’s fingers to collect objective reading of skin temperature. After two minutes of baseline recording, the ultrasonic noise was played. Participants then reported how much they were attending to temperature change and also provided
estimates of actual temperature. The data supported the hypothesis that the reporting of somatic sensations (finger temperature) would verify their expectations about the effects of the ultrasonic noise. Patients in the increase condition reported attending more to increases in skin temperature and less to sensations of decreasing temperature. The opposite was true for in decrease condition. Despite no actually differences in skin temperature across the groups, participants in the increase condition reported their fingers becoming warmer after exposure to the noise, whereas participants in the decrease condition reported their fingers getting colder. Moreover actual fluctuation in skin temperature was interpreted in accordance with participant’s manipulated schema. A positive correlation was found between objective skin temperature fluctuation and self-reported skin temperature for participants in the increase condition, whereas in the decrease condition a negative correlation was evident. This suggests that pre-existing cognitive schema influenced the selection and reporting of somatic sensations. Furthermore, a perceived change in temperature was interpreted in different ways in accordance with underlying cognitive schema (Pennebaker, 1982; Pennebaker & Skelton, 1981).

3.3.3 Content of Illness Representations

As described above, the construction of illness representations relies upon the perception and interpretation of both semantic and concrete processes. The substance of illness representations and their bi-level nature sets the CSM apart from other models of health behaviour such as the theory of planned behaviour and the health belief model. Indeed, it is the representation of illness that serves as the self-regulatory target that defines goals, and provides the reference values for regulation (Brownlee, Leventhal, & Leventhal, 2000). The content of illness representations has received the majority of empirical enquiry, and is the focus of the work to be reported in this thesis.

Early in the development of the CSM, symptoms were identified as a core domain. In order to further understand the attributes of illness representations several approaches were undertaken in patient and student samples, including open ended interviews (Lau, Bernard, & Hartman, 1989; Lau & Hartman, 1983), multidimensional scaling and factor analysis.
(Bishop & Converse, 1986, 1991). Results from these investigations reveal that illness representations consisted of five illness perceptions:

1) **Illness identity** – Symptoms and labels of disease and the subsequent joining of these.

2) **Time-line** – Perceived length of the illness, either short-term (acute), chronic, or cyclical.

3) **Consequences** – Reflects perceived illness severity and the associated social, physical and psychological consequences of the illness.

4) **Causes** – Patients beliefs about what caused the illness (e.g. germ or virus or one’s own behaviour.

5) **Controllability** – Perceptions of whether the illness can be controlled or cured.

While the nature and relative importance of illness representations may be disease specific (Heijmans & de Ridder, 1998) several reviews of illness representations, notably the meta-analysis conducted by Hagger and Orbell (2003) confirm the five factor structure of illness representations (Kaptein et al., 2003; Scharloo & Kaptein, 1997b; Skelton & Croyle, 1991). Illness perceptions share logical inter-relationships (Hagger & Orbell, 2003), thus instead of operating as single cognitions, they coalesce to form an illness representation. The development of the Illness Perception Questionnaire (Weinman, Petrie, Moss-Morris, & Horne, 1996), and the Revised Illness Perception Questionnaire (Moss-Morris et al., 2002) has allowed researchers to assess illness perceptions using standardised methods (see general methods). Moreover, the development of these questionnaires has provided further evidence for the content of illness representations (Moss-Morris et al., 2002; Weinman et al., 1996).

The content of illness representations and subsequent self-regulatory processes are not isolated from personal, social and culture factors. Prior illness experience will provide procedural and episodic memories which would act as heuristics following a similar illness episode. Individual differences regarding symptom perception is another factor that may influence the development and depth of a person’s illness representation (c.f Pennebaker,
Social and cultural practices have a considerable influence upon the nature of illness representations and the respective action plans employed to overcome health threats. It is clear that cultural factors influence abstract perceptual knowledge regarding illnesses, but also how symptoms are attended to and reported (Brownlee et al., 2000). For example in the Chinese culture psychological symptoms are often down played due to a stigmatisation of psychological distress (Kleinman, 1980), thus conditions such as depression and anxiety are often under recognised or misdiagnosed as a physical condition. In addition the social environment is a critical source of information when faced with a health threat. Individuals often approach friends and family first when faced with an illness threat. Social comparison is also a critical part of the cognitive adaption to illness (Taylor, 1983), and is likely to influence personal illness representations.

### 3.3.4 Illness Representations guide action and procedures: IF-THEN rules

The CSM posits that illness representations guide action and procedures to regulate health threats (Leventhal et al., 1998; Leventhal et al., 1980). However the treatment of “coping” in the CSM deviates from factor analytic approaches such as the stress coping model (Lazarus & Folkman, 1984). Such approaches attempt to generalise how people cope with emotions yet ignore the specific content of the threat and how procedures (action plans) are selected in response to deal with them (Leventhal et al., 2003; Leventhal et al., 1992). In the CSM, coping procedures refer to the “cognitive and behavioural actions we take (or do not take) to enhance health and to prevent, treat (i.e. cure or control), and rehabilitate from illness” (Leventhal et al 1998, pp 772).

Following the onset of a headache there are numerous “problem based” actions individuals employ including, taking analgesics or applying a cold cloth to the forehead. The representation of the headache, including its cause (i.e. stress or excessive alcohol intake), and expected or actual time-line (week long or a few hours) will shape the specific procedures undertaken to control it. Procedures are goal-relevant and related to outcome expectations (will doing X control Y? Bandura 1977). In addition, procedures have organised representations regarding their identity, time-line for action, cause, controllability and consequences. For example during a perceived stress-headache, one may decide to take an analgesic which is expected to alleviate the pain within 30 minutes (Brownlee et al., 2000).
If after this period the headache remains the representation maybe updated to reflect a more serious underlying health condition (consequences, timeline, and causes), thus requiring medical attention. Moreover, the use of medications also depends of specific cognitions surrounding them (Horne, 1997; Horne & Weinman, 1999, 2002). Perceptions regarding the concerns and necessity of medication have been shown to predict adherence (Horne & Weinman, 1999). If our headache sufferer is averse to taking a drug (i.e. due to side effects) they may instead take rest or take herbal remedies. Therefore specific health care behaviours are dependent upon the coherence between the illness representation and the procedures selected to deal with the threat. This is described as “IF-THEN” rules (Anderson, 1983; Brownlee et al., 2000; Leventhal et al., 2003). IF refers to the interpretation of the illness threat (targets for self-regulation); Then refers to the procedure and actions undertaken to tackle the threat.

IF-THEN rules are the moderators and mediators in the CSM. Several heuristics have been suggested that provide detailed elaboration of the IF-THEN process. These heuristics aid the individual in the evaluation of illness indicators to determine “am I ill?” and “what should I do?” The first of these rules, the symmetry rule, has been described above. The prevalence rule simply refers to the perception that an illness is more severe the less common it is perceived to be (Kahneman & Tversky, 1973). For example, in one experimental study participants who believed they were the only person in a group to test positively for a fictitious antigen that was indicative of increased cancer risk, were more likely to report the disease as severe as compared to a group of individuals that were told they were all positive “carriers” (Croyle & Jemmott, 1991). The stress-illness rule refers to attribution of symptoms (illness) to stress. Accordingly individuals under condition of acute stress are like to attribute ambiguous somatic symptoms as products of their stress and avoid care seeking behaviour (Cameron, Leventhal, & Leventhal, 1995). The duration rule simply refers to the positive association between perceived severity of illness and symptoms duration. Indeed, the length of symptoms exposure predicts health seeking behaviour (Mora, Robitaille, Leventhal, Swigar, & Leventhal, 2002). The age-illness rule reflects a tendency with age to misattribute somatic symptoms as processes inherent with ageing, resulting in delays in seeking health-care (Croyle & Jemmott, 1991; Leventhal et al., 2003).
While it is likely that more heuristics exist, these rules appear to be important in the initial interpretation of an illness threat. Quite how these rules operate within the context of chronic illnesses, such as ESRD, remains to be elaborated.

3.3.5 Illness Schema

Illness schema exists within a cognitive framework, which guides the selection of illness related information. As initially conceived in the CSM individuals hold schemata for acute, chronic and cyclical conditions. Leventhal et al (1980) describe how coping procedures are encoded within illness schema. Indeed this is implicit in IF-THEN rules described previously. However few studies have explicitly examined the schematic nature of illness representations. Henderson, Orbell & Hagger (2009) addressed this need by conducting a series of experiments investigating illness schema and coping procedures associated with the common cold. In a 2 (prime vs. control) X 2 (past users of lozengers vs. nonusers) design, participant latencies for correct responses on a grammatical decision task (a common cold remedy) were measured. Participants who were experimentally primed for illness words relating to the common cold, and who were also past users of a specific coping procedure (e.g. lozeneger takers) showed an attentional bias for a common cold remedy reflected in longer response times. There was no significant main effect of the prime, or whether the participant was a past user of such remedies, or not. These results suggest that the past successful use of a coping procedure becomes encoded within the illness schema (Henderson, Orbell, & Hagger, 2009). The future activation of the illness schema may automatically activate the encoded coping procedures (within episodic and working memory). Moreover this reinforces the main tenets of the CSM: that is, illness representations set the goals for self-regulation and are not static trait like attitudes but instead dynamic perceptions amenable to change.

3.4. Representations of Physical Illness

Much of the theoretical and development strides in the CSM have been achieved by assessing individual reactions to new health threats, and the behaviours people adopt as a part of the self-regulation of health and illness. The CSM has also received considerable attention among chronic illnesses, particularly the nature and content of illness representations and how these relate to clinical and psychological outcomes. A synthesis
of this literature can be found in the following sources (Hagger & Orbell, 2003; Kaptein et al., 2003; Skelton & Croyle, 1991). In summary, a wealth of research has shown that illness representations predict health-related outcomes. For example, perceptions of increased time-line and illness consequences predict illness related disability and slower return to work following a myocardial infarction (Petrie, Weinman, Sharpe, & Buckley, 1996), and perceptions of control predict attendance at cardiac rehabilitation clinics (Cooper, Lloyd, Weinman, & Jackson, 1999). There is convincing evidence that illness representations predict functional status and quality of life over time (Bijsterbosch et al., 2009; Graves, Scott, Lempp, & Weinman, 2009; Kaptein et al., 2010; Scharloo et al., 2000), and also psychological outcomes (Sheldrick, Tarrier, Berry, & Kincey, 2006). Furthermore illness perceptions are associated with a range of adherence and care-seeking behaviours (Hampson, Glasgow, & Toobert, 1990; Jessop & Rutter, 2003; Lawson, Bundy, Lyne, & Harvey, 2004; Scharloo et al., 1998; Scharloo et al., 1999; Whitmarsh, Koutantji, & Sidell, 2003). There is comparatively less data examining the change in perceptions over the course of a disease (Fischer et al., 2010), although a few studies have shown that timeline and illness coherence perceptions increase over time, and emotion and perceived control perceptions decrease over time (Bijsterbosch et al., 2009; Lawson, Bundy, & Harvey, 2008). Furthermore changes in perceptions over time have been shown to predict functional outcomes in osteoarthritis (Kaptein et al., 2010) suggesting there may be some dynamic relationship between illness perceptions and outcomes among patients with chronic physical disease.

The dynamics of illness perceptions over time is discussed in more detail later on (chapter 8). Instead a narrative review to follow will focus on studies that have assessed illness representations and depression employing both cross-sectional and longitudinal designs. In addition literature specific to ESRD is overviewed. I will finish this review section by describing intervention studies that have attempted to alter maladaptive illness representations in order to improve health-related outcomes.

### 3.4.1 Illness Representations and depression

Negative perceptions of illness have largely been associated with health-related behaviours, functional disability, and psychological wellbeing (QoL). Fewer studies have
specifically investigated illness perceptions and depression using conventional assessments specific to depressive symptoms (i.e. the BDI). Several studies have examined the cross-sectional association between depression and illness representations. A study of Rheumatoid Arthritis (RA) patients revealed that depression correlated positively with consequence perceptions, and negatively with control/cure perceptions, findings which were upheld after controlling for disease severity (Murphy, Dickens, Creed, & Bernstein, 1999). The relationship between illness perception, depression and gender was the focus of one study in CVD patients (Grace, Krepostman et al., 2005). Males had significantly weaker perceptions of time-line and cyclical perceptions, and stronger perceptions of personal and treatment control compared to females. In males, depression symptoms were predicted by time-line perceptions, consequences and treatment control. The only illness perception associated with depression symptoms in females was stronger time-line beliefs. However, given that depression scores did not vary with gender it is important not to over stress the impact of gender upon illness perceptions from this data.

Jopson & Moss-Morris (2003) examined the impact of illness representations in adjusting to Multiple Sclerosis (MS). Illness perceptions as assessed by the IPQ-R were significantly related to adjustment in a sample of 180 MS patients. Although illness severity predicted the most variance in physical disability, illness representations were strongly associated with fatigue, anxiety and depression. After adjusting for clinical and demographic variables, a lower perception of personal control, greater perceived consequences and perceptions of psychological causes predicted HADS- depression scores (Jopson & Moss-Morris, 2003).

While there is convincing evidence that illness representations and depression are associated across a spectrum of physical diseases, the cross-sectional nature of these studies prevents the temporal relationship between depression and illness perceptions from being inferred. Negative illness perceptions may be the consequence of negative illness schema activated in depressed individuals, or may serve as a cognitive vulnerability for depression in patients with physical illness (Beck, 1967).

One of the first longitudinal investigations assessed the relationship between illness representations and psychological adjustment in patients with RA and MS (Schiaffino, Shawaryn, & Blum, 1998). Depression was assessed using the Center for Epidemiologic
Studies Depression Scale and illness representations by the Implicit Models of Illness Questionnaire (IMIQ). In both patient groups illness representations were not associated with concurrent depression but did predict a change in depressive symptoms over time (Schiaffino et al., 1998). In RA patients both curability and personal responsibility perceptions predicted later depression, whereas a stronger perception that symptoms varied from day to day was predictive of depression in the MS sample. Moreover, there was an interaction between disease status and consequences perceptions for predicting depression in patients with RA suggesting that dynamic relationship between disease status and illness representations. Illness representations have also been found to predict depression following a surgical intervention for osteoarthritis (Orbell, Johnston, Rowley, Espley, & Davey, 1998). Higher preoperative control perceptions predicted depression at 3 months post surgery. Causal attributions and outcome expectations predicted depression 9 months post surgery (Orbell et al., 1998). Interestingly, social and demographic factors were not associated with depression suggesting the illness representations had an independent effect upon mood.

More recent data reports that new-onset depression is associated with illness perceptions assessed days after a MI (Dickens et al., 2008). After considering covariates including measures of cardiac disease severity (Killip Class), chronicity and control perceptions predicted new-onset depression (Dickens et al., 2008). A recent investigation reports that illness perceptions before cardiac surgery predict depression and disability 3 months later (Juergens, Seekatz, Moosdorf, Petrie, & Rief, 2010). Similarly, stronger time-line perceptions in patients with head and neck cancer have been shown to predict depression 6-8 months post-treatment (Llewellyn, McGurk, & Weinman, 2007). A study in patients with atrial fibrillation utilised growth modelling, which is a more robust method for handling longitudinal data (Lane, Langman, Lip, & Nouwen, 2009). The results revealed that baseline illness perceptions did not contribute to the growth trajectory of depression symptoms. However it should be noted that depression symptoms were remarkably low and stable in this patient group (Lane et al., 2009).

Despite the longitudinal designs of the above studies, most only used a single baseline measurement of illness perceptions for predicting future outcomes. Critically this does not tell us how the illness representation changed over time in relation to outcome measures.
such as depression. Multiple measures of illness perception are therefore required in order to evaluate the potentially dynamic relationship with depression over time.

**3.4.2 Illness Representations in ESRD**

A summary of studies that have examined illness representations (as pertains to the CSM) in relation to psychological, social or clinical outcomes in ESRD are shown in table 3.1. Eight studies were identified after searching *PubMed, Psycinfo*, and the *Web of Knowledge* databases, using the search term “illness representations” and “ESRD”. An additional term “illness perceptions” was entered in subsequent searches.

Five of the identified studies addressed the relationship between illness representations and Quality of Life (QoL), all of which report an association between illness representations and QoL in ESRD, although these studies differed in their methodological approach. All but one (Fowler & Baas, 2006) employed the SF-36 to measure health related QoL. In the largest most controlled study reviewed Griva et al (2009) report that treatment and illness cognitions are associated with QoL. After controlling for demographic and dialysis related factors, both perceptions of treatment disruptiveness and illness consequences were associated with the mental functioning component of the SF-36. Timmers et al (2008) reported that illness identity, consequences, personal control, and emotional representations, were associated with the physical component score of the SF-36, explaining an additional 30% of the variance above and beyond clinical and demographic variables. Mental QoL functioning was predicted by emotional representations and illness coherence, which uniquely explained 42% of the variance (Timmers et al., 2008). However the cross-sectional nature of these studies prevents the temporal relationship between QoL and illness representation from being inferred. Only one study has explored illness representations and QoL over time in dialysis patients. Covic et al (2006) followed HD patients over two years and reported that emotional representations reduced over time, whereas illness coherence and perceptions of treatment control increase. Moreover baseline illness representations predicted improvements in QoL. Higher personal control and illness coherence, and lower emotion representations at time one predicted improved physical QoL scores at time 2. Lower baseline consequence scores were associated with improvements in mental QoL functioning. Despite the relatively small sample size, only two
time points, and a lack of consideration of extra-renal co-morbidity, these results suggest that illness representations are dynamic and are associated with changes in QoL in HD patients.

The utility of understanding illness representations in ESRD extends beyond QoL. Treatment and illness perceptions have been associated with measures of non-adherence in dialysis patients (Butler et al., 2004; O’Connor, Jardine, & Millar, 2008). O’Connor et al. (2008) found that emotional representations and time-line perceptions explained an additional 16% of the variance in serum phosphate², after controlling for demographic and clinical factors. A recent study examined whether illness representation predicted mortality in a sample of dialysis patients followed up for mean of 3.5 years (van Dijk et al., 2009). In adjusted survival analysis lower treatment control perceptions were significantly associated with increased mortality risk, although depression was not assessed and hence not controlled for in the analysis which may be a potential confound. Nevertheless it is suggested that lower treatment perceptions may influence self-care and non-adherence behaviours, which in turn may impact upon survival.

These studies all examined the full content domains of illness representations according to the CSM. However by casting the net a little wider and looking at similar concepts, there is further evidence that perceptions pertaining to illness are associated with QoL, adherence and depression in ESRD. For example as reviewed in chapter 2, perceptions of control and illness intrusiveness are associated with depression in ESRD. Similarly greater internal health locus of control and lower emotion-focused coping correlates with QoL in PD patients (Pucheu, Consoli, D’Auzac, Francais, & Issad, 2004). Further, perceptions of self-efficacy and health locus of control have been associated with non-adherence behaviour in ESRD (Karamanidou, Clatworthy, Weinman, & Horne, 2008; Schneider, 1992; Zrinyi et al., 2003).

² Serum phosphate can be used as a clinical proxy measure of non-adherence to phosphate-binding medications. Higher levels of serum phosphate suggest non-adherence to the medication.
In summary, there is a relative lack of research that has examined the associations between illness representations (CSM) and outcomes in ESRD. The current empirical landscape, albeit limited, has shown that illness representations are associated with QoL, mortality, and non-adherence in ESRD. While it is clear than more research is required to confirm these findings, no studies have examined the impact of illness representations upon depression in ESRD. As reviewed in the previous chapter depression is a common yet complex psychopathology in dialysis patients. How illness representations impact upon depression in ESRD is unknown and is the focus of the subsequent works to be reported in this thesis. It is known that that depression is treatable, although certain challenges arise when treating depression among chronic physical illnesses. Furthermore, illness representations are amenable to psychological intervention and improve health related outcomes, which are briefly reviewed in the following section.

3.4.3 Changing illness perceptions: Interventions

The CSM provides a theoretical platform from which adaption to, and management of physical illnesses can be evaluated. However there have been few studies that have utilised the CSM in order to influence this process and to potentially improve health-related outcomes (McAndrew et al., 2008). Previous studies in myocardial infarction patients revealed that illness perceptions predicted functional disability, the time it took to return to work (Petrie et al., 1996), and attendance at cardiac rehabilitation (Cooper et al., 1999). A landmark study investigated whether altering maladaptive illness perception soon after an MI led to improvements in health-related outcomes (Petrie et al., 2002). An in-hospital intervention was developed and administered at a point soon after MI. The intervention involved three sessions with a psychologist, and was individualised for each patient following their response on the IPQ. The sessions involved explaining the physiology of MI using concrete images, exploring personal illness perceptions, dispelling misconceptions, exploring self-care behaviours and developing an action plan to reducing future risk. Patients were randomised to receive either the intervention or standard nurse lead education. The results revealed that the intervention significantly altered illness perceptions pertaining to time-line and control-cure perceptions as measured by the IPQ three months post MI. As compared to the control group, intervention patients returned to work significantly sooner and reported fewer angina symptoms (Petrie et al., 2002).
Table 3.1: A review of studies that have examined Illness Representations in End-Stage Renal Disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>Objectives</th>
<th>Methods</th>
<th>Results</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td>(van Dijk et al., 2009)</td>
<td>Explored whether illness perceptions of ESRD are related to mortality.</td>
<td>182 dialysis patients assessed by IPQ-R</td>
<td>61 deaths. Weaker perceptions of treatment control associated with increased mortality risk (Adjusted OR=0.65 95% CI 0.46-0.92).</td>
<td>Patient’s personal illness beliefs are predictive of mortality in ESRD patients.</td>
</tr>
<tr>
<td>(Griva et al., 2009)</td>
<td>Explored whether treatment and illness beliefs differed between dialysis and transplant patients, and to examine which beliefs are associated with QoL</td>
<td>Cross-sectional. 145 dialysis and 117 kidney transplant patients.</td>
<td>Transplant patients had better QoL as compared to dialysis patients. Dialysis patients had higher illness identity, time-line and lower perceptions of control</td>
<td>Illness beliefs differ between dialysis and transplant patients.</td>
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<td></td>
<td></td>
<td>Questionnaires: IPQ, IEQ, TEQ and a QoL measure the SF-36</td>
<td>In regression analysis treatment and illness beliefs accounted for 22.9-67.6% of the variance in QoL (SF-36).</td>
<td>Illness cognitions predict health related QoL in ESRD.</td>
</tr>
<tr>
<td>(O'Connor et al., 2008)</td>
<td>Explored whether the CSM predicted non-adherence.</td>
<td>Cross-sectional assessment of IPQ-R and brief COPE (n=73)- 3 week follow-up (clinical data).</td>
<td>In multiple regression analysis emotional representations predicted dietary adherence (K), and both emotion and timeline perceptions predicted drug adherence (PO4).</td>
<td>Despite small effect, illness perceptions predicted facets of non-adherence in ESRD above and beyond clinical and demographic factors.</td>
</tr>
<tr>
<td>(Timmers et al., 2008)</td>
<td>Examined the relationship between illness representations and QoL.</td>
<td>Cross-sectional. 91 HD and 42 PD patients completed the IPQ-R and the SF-36.</td>
<td>HD patients held weaker perceptions of control and coherence as compared to PD. 17-51% of QoL variance explained by illness representations.</td>
<td>Illness representations differ across ESRD treatment modalities, and are associated with QoL.</td>
</tr>
<tr>
<td>(Fowler &amp; Baas, 2006)</td>
<td>Assessed the relationship between illness representations and QoL.</td>
<td>Cross-sectional. 42 HD patients completed IPQ-R and a QoL measure (IWB).</td>
<td>Consequences and emotion correlated negatively with QoL.</td>
<td>Illness perceptions have a moderate univariate association with QoL.</td>
</tr>
<tr>
<td>Study</td>
<td>Objectives</td>
<td>Methods</td>
<td>Results</td>
<td>Conclusions</td>
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<td>(Covic, Seica, Mardare, &amp; Gusbeth-Tatomir, 2006)</td>
<td>Explored the longitudinal relationship between QoL and illness representations.</td>
<td>81 HD patients followed up over a two-year period. Assessed on the IPQ-R and SF-36.</td>
<td>Multivariate regression revealed that baseline control, emotion, and coherence perceptions predicted a change in the physical component SF-36 score, after controlling for baseline QoL. Baseline consequence perception scores predicted a change in mental component scores.</td>
<td>Illness representations are associated with a change in QoL in HD patients.</td>
</tr>
<tr>
<td>(Covic et al., 2004)</td>
<td>Examined the relationship between illness representations and QoL in HD patients, with dialysis vintage.</td>
<td>Cross-sectional. 82 HD patients completed the IPQ-R and the SF-36.</td>
<td>Emotional representations correlated negatively with treatment duration. Greater time-line perceptions and lower emotion predicted SF-36 physical component score. Greater personal control and lower emotion predicted SF-36 mental component score.</td>
<td>Illness perceptions are associated with QoL, although the regression analysis did not control for demographic and clinical factors.</td>
</tr>
<tr>
<td>(Butler et al., 2004)</td>
<td>Examined the relationship between depression, treatment and illness perceptions with adherence to anti-rejection medication.</td>
<td>58 transplant patients. 6 week electronic monitoring of drug taking (&gt;20% of days missed = non-adherent.</td>
<td>In logistic regression analysis, live donor transplantation, and low necessity beliefs regarding the medication predicted non-adherence.</td>
<td>This small study suggests that treatment perceptions predict non-adherence. No specific illness perception predicted non-adherence.</td>
</tr>
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</table>

A recent study extended the scope of this early intervention study in MI patients by broadening the definition of MI based upon the cardiac enzyme troponin T (Broadbent, Ellis, Thomas, Gamble, & Petrie, 2009). One hundred and three MI patients were randomised to receive an illness perception intervention or standard care. The intervention successful changed causal attributions of MI and increased patients understanding of the condition (illness coherence). As with the earlier study (Petrie et al., 2002) the intervention group returned to work faster, reported more use of exercise, and lower anxiety about returning to work (Broadbent et al., 2009). The authors suggest that the intervention altered different illness representations than those identified in the Petrie et al (2002) study due to the broader sample of MI patients studied based upon troponin T levels. Nevertheless both sets of data show that targeting maladaptive illness perceptions can improve health related outcomes following an MI.

A pilot of a psycho-educational intervention in dialysis patients, designed to improve understanding of the need for phosphate control revealed promising results (Karamanidou, Weinman, & Horne, 2008). As compared to controls, patients who received the intervention reported improved knowledge regarding their phosphate binders and greater outcome efficacy throughout the study follow-up. Although the study was not powered to detect improvements in phosphate control, the findings suggest that psychological interventions can improve patient perceptions towards a defined behaviour in this setting.

3.5 Concluding Remarks

Illness representations are activated following an illness threat and are maintained throughout the illness experience. They provide a mental interpretation of the illness, and guide the selection and adoption of health behaviours as a part of a dynamic self-regulatory model (CSM). In this chapter the main tenets of the CSM have been described and the specific content of illness perceptions defined. After an examination of the current literature several points can be inferred:

1) Illness representations are associated with a range of health-related outcomes including, adherence, functional status and QoL.

2) Illness representations, particularly consequences, timeline and control are associated with depression across several disease states.
3) Preliminary studies in ESRD suggest the utility of Illness representations in explaining adherence, QoL and mortality albeit with a greater need for investigation.

4) Illness representations are amenable to psychological intervention and improved health outcomes.

The main issue across the literature is lack of longitudinal measures of illness representations in order to establish variation over time. Indeed the regulation of illness representations is cardinal to the CSM, yet is not a feature in most empirical studies (Fischer et al., 2010; Kaptein et al., 2010). In the studies reported in the following chapters the relationship between illness representations and depression is explored in both cross-sectional and longitudinal samples of dialysis patients. In addition the relationship between illness representations and depression with outcomes (adherence and mortality) is also evaluated. I will argue that illness representations are essential components related to depression and health-related outcomes in individuals with ESRD.
Chapter 4

General Methods

4.1 Introduction

Methodological features that pertain to all the subsequent empirical work to follow are described in the present chapter. The first section provides a rationale for the study designs and considers the patient population investigated. The questionnaires common to each of the empirical chapters are then described. Specifically, these are the Beck Depression Inventory-II (BDI) and the Revised Illness Perception Questionnaire (IPQ-R). The assessment of co-morbidity, functional performance and the collection of clinical data are also considered. The final section regards the statistical methods employed in parts of the analysis that follow, with an emphasis on structural equation modelling (SEM) techniques. An overview of SEM and relevant techniques is presented, as an in-depth discussion of the technique is beyond the scope of this chapter. In addition to SEM, other statistical approaches that feature are described.

4.2 Design Rationale

The empirical studies presented in this thesis emerge from two large multi-center studies of illness representations and depression symptoms in dialysis patients. The majority of the literature surrounding illness representations are largely limited to cross-sectional studies. While such studies allow the association between depression and illness perceptions to be determined, they cannot infer temporal relationships between the constructs. In addition, there is a paucity of longitudinal data considering the course of depression in ESRD and its predictors, and studies that have tended to use panel designs have often only two time points (i.e. baseline and one follow-up).

In order to address these needs and to examine the potentially dynamic relationship between illness representations and depression, a multi-centred three-wave panel design study was conducted. In addition to the longitudinal sample, a large cross sectional study was undertaken. The rationale and description of these designs follows below.
4.2.1 Cross-sectional study

A large cross sectional study was undertaken to assess depressive symptomatology and illness representations among established haemodialysis patients. Not only does this exploration provide data on the prevalence of significant depression symptoms in this population, but also serves as a comparator to the longitudinal data. Further it allows the association between illness perceptions and depression in other illness groups to be explored in this patient setting, and promotes comparisons across patient populations. That is, is depression related specifically to facets of illness or rather due to the psychological interpretation and regulation of the disease as posited in the CSM.

In addition the cross-sectional investigation provided a significant amount of BDI data, which could be combined with a selection of data from the longitudinal study in order to conducted relevant analyses to examine the BDI’s underlying factor structure using Confirmatory Factor Analysis (CFA). This is important given the current lack of data concerning the factorial structure of the BDI in ESRD and the broader issues of assessing depression in the context of physical disease.

4.2.2 Longitudinal Study

A longitudinal study design was employed in order to evaluate the change in depression symptoms over the first year of dialysis, and to identify relevant illness perceptions that are associated with such change. The benefits of following individuals up not only allows changes over time and predictors of change to be identified, it also allows individual variability through the employment of more advanced statistical methods (Latent Growth Modeling) to be evaluated.

Initiating dialysis patients were assessed within the first three months of treatment, and again at six and twelve months later (figure 4.1). Screening dialysis patients for depression 3-6 months after dialysis initiation and again at a year has been recommended by several authors (Hedayati et al., 2006; Hedayati & Finkelstein, 2009). The three-wave panel design employed in the longitudinal study conforms to this recommendation, and allows the course of depression and it’s antecedents to be identified over the first year of dialysis. Furthermore three time points also allows a closer examination of the trajectory of change
over time. A description of the study follow-up with regards to patient recruitment and attrition is described in methods section of chapter 8.

Figure 4.1: Pictorial representation of the three-wave panel design.

4.3 Patients

All of the patients recruited in the work to follow had ESRD treated with dialysis. The majority of dialysis patients were recruited from the renal service of the East and North Hertfordshire NHS trust (Lister Hospital and two satellite units based in St Albans and Luton-Dunstable Hospitals). In addition patients were recruited from the renal service of Addenbrooke’s Hospital, and the Royal Free Hospital (including the satellite unit at St John and Elizabeth’s Hospital). All patients were recruited providing they satisfied the following criteria; i) no known significant visual or physical impairment that would prevent the completion of the questionnaires, ii) fluency in verbal and written English language\(^3\), (iii) not hospitalised at the time of assessment and iv) no cognitive impairment, as indicated by an age adjusted score of <22 on the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975). Inclusion criteria that pertain to particular studies are presented in the relevant chapters accompanied by consent rates. NHS ethics and local Research and Development approval was sought for each study. All patients provided informed consent and were given a minimum of 24 hours to consider participation. Copies of the ethics approval letters are shown in the appendix.

\(^3\) The BDI is not easily translatable and the construct of depression in non-western cultures remains largely undefined. For these reasons the studies were restricted to English speaking patients.
All but one of the investigations that follow exclusively studied patients receiving in-hospital HD. It was decided to focus on this treatment group for the following reasons; 1) HD is the most common form of renal replacement therapy, 2) there is limited published data to suggest that depression would vary across HD and PD modalities, and 3) increased accessibility to the HD patient population.

4.4 Haemodialysis

There were some differences between the haemodialysis programmes in the 3 participating centres:

4.4.1 Lister Renal Unit

Patients were treated exclusively using high flux membranes, predominantly polysulphone. Approximately forty percent of patients were treated by on-line haemodiafiltration (HDF). Bicarbonate was used exclusively as the buffer. Water quality was regularly monitored to ensure tight bacteriological standards (<0.1 cfu/mL and <0.03 EU/ml). Dialysis was prescribed and monitored according to a target two-pool total Kt/V of 1.2 (dialysis plus residual renal function) per dialysis session for thrice weekly dialysis. Adequacy monitoring was carried out monthly and included estimates of residual renal function (as kidney urea clearance – KRU).

4.4.2 Addenbrooke's Renal Unit

Patients were treated exclusively using high flux membranes. Bicarbonate was used as the buffer. Water quality was regularly monitored to ensure tight bacteriological standards. Dialysis was adequacy was monitored every three months with a target single-pool Kt/V of 1.2.

4.4.3 Royal Free Center for Nephrology, UCL

Patients were treated exclusively using high flux polysulphone membranes. Approximately six percent of patients were treated by on-line haemodiafiltration (HDF). Bicarbonate was used exclusively as the buffer. Ultrapure water, which is free of chloramines, is used as standard. Dialysis was prescribed and monitored according to a target minimum single pool on-line Kt/V of 1.4 per dialysis session for thrice weekly dialysis. Adequacy monitoring was carried out monthly and included estimates of residual renal
function (KRU). Patients with significant residual renal function often have once a week or twice a week dialysis (<0.1% of patients with a weekly KRU of >1.0 receives 3x week HD).

4.5 Questionnaire methods

4.5.1 The Assessment of Illness Representations

The conceptualisation of illness representation evolved from fear communication studies, adopting predominantly qualitative research methods. Since Leventhal’s early work, a plethora of studies have been conducted investigating illness perceptions utilising both qualitative and quantitative approaches (Hagger & Orbell, 2003; Scharloo & Kaptein, 1997a). Leventhal’s seminal work focused on in-depth semi-structured interviews, of which the emphasis was on the concrete aspects of the illness experience (Leventhal et al., 1980). However while of value, interviews are time consuming thus not suited to particular study designs or indeed hypothesis-driven research. As noted elsewhere there is no psychometric evidence regarding eliciting illness representations via interviews (Weinman et al., 1996). A novel approach still in its infancy concerns pictorial representations of disease (e.g. drawings of hearts following a myocardial infarction), which have been shown to be associated with health-related outcomes (Broadbent, Ellis, Gamble, & Petrie, 2006; Broadbent, Petrie, Ellis, Ying, & Gamble, 2004). Although this method requires further evaluation, is this clear that such an approach may have utility in groups of patients where language barriers prohibit conventional assessment.

Several questionnaires have been employed to assess illness representations (Hagger & Orbell, 2003) although the vast majority of these were not specifically designed for the purposes of measuring the five cognitive representations of illness (identity, timeline, control/cue, consequences and causes), and were not validated across illness groups. The need to develop a theoretically derived validated method of assessing illness representations was realised by John Weinman and colleagues (Weinman et al., 1996). The Illness Perception Questionnaire (IPQ) was the first attempt to systematically assess the core cognitive facets of illness representations, as developed across several illness groups (Weinman et al., 1996). The questionnaire consists of five dimensions each assessing a component of illness representations on a likert type scale. Although the IPQ prompted the rapid expansion of research into the self-regulation of health and illness, it was clear that
there were a few psychometric issues with the IPQ. Additionally the IPQ did not consider emotional representations, which is a significant feature of the CSM regarding an individual’s emotional reaction to illness threats. These issues were addressed in the development of the Revised Illness Perception Questionnaire (IPQ-R) (Moss-Morris et al., 2002), which is employed in the empirical studies that follow.

**4.5.2 The Revised Illness Perception Questionnaire (IPQ-R)**

The IPQ-R (Moss-Morris et al., 2002) was derived from eight illness groups (n=711) using factor analysis. The revised questionnaire has a number of improvements with regards to its treatment of illness identity, timeline, control/cure perceptions and causal attributions. Illness identity consists of 14 common illness symptoms, in which the patient has to rate whether they have first experienced the symptoms (yes/no), and then if so do they attribute the symptoms to their illness (i.e. their kidney problem). The sum of the *attributed* symptoms forms the IPQ-R identity subscale (scoring 0-14). This structure avoids potential somatisation of symptoms possible in the original IPQ, as symptoms were rated on an intensity scale, which may reflect symptom perception rather than the concept of illness identity (Moss-Morris et al., 2002). Furthermore the IPQ-R distinguishes cyclical time-line perceptions from acute/chronic time-line perceptions, thus contains two respective subscales to reflect this. The addition of an emotional subscale in the IPQ-R allowed the consideration of individual’s emotional response to illness. These items were derived from previous data (Cameron, Leventhal, & Leventhal, 1993). Causal items were extended from 10 (IPQ) to 18 (IPQ-R), although the authors recommend conducting exploratory factor analysis in order to establish underlying causal factors. An illness coherence subscale was added to assess patients overall understanding of their condition. Further, factor analysis of the original IPQ items suggested that the control/cue dimension loaded onto two separate factors 1) treatment control and 2) personal control. These factors were developed and incorporated into the IPQ-R. Moss-Morris et al (2002) conducted a principle component analysis (PCA with varimax rotation) on 50 items pertaining to the time-line, control, consequences, illness coherence and, emotion representation scales. After the removal of multi-loading items, and non significant loadings, 38 items produced a total of seven factors, accounting for 64% of the variance (*Consequences*, *Emotional*, *Timeline*, *Cyclical timeline*, *Illness coherence*, *Personal Control*...
and Treatment Control). All of these illness perception factors are measured on a five point Likert scale (strongly disagree - strongly agree); Consequences (e.g. “my kidney problem has major consequences on my life”), Emotional representations (e.g. “I get depressed when I think about my kidney problem”), Timeline (e.g. “my kidney problem will last for a long time”), Cyclical timeline (e.g. “my symptoms come and go in cycles”), Illness coherence (e.g. “my kidney problem is a mystery to me”), Personal Control (e.g. “I have the power to influence my kidney problem”) and Treatment Control (e.g. “my treatment can control my kidney problem”). High scores on the timeline and consequences dimensions reflect strongly held beliefs about the chronicity and negative consequences of the condition and the cyclical dimensions reflect strongly held beliefs that the condition is cyclical in nature. High scores on the personal control, treatment control and coherence sub-scales reflect strong perceptions of illness controllability and a greater personal understanding of the condition. The IPQ-R as used in the studies to follow can be found in the appendix.

Although the IPQ-R was developed and tested in a rigorous manner by Moss-Morris et al (2002) a more robust method to evaluate the questionnaires constructs and discriminant validity is CFA. Hagger & Orbell (2005) conducted a CFA of the IPQ-R in patient undergoing cervical screening and report that the factor model could be reproduced adequately from their sample data. After removing two items responsible for model misspecification, good model fit was demonstrated. Furthermore, the inter-correlations between the latent variables supported those found in previous studies and their discriminant validity (Hagger & Orbell, 2005).

4.5.3 Scoring the IPQ-R

The IPQ-R was scored according to the instructions available on the Illness perception website (http://www.uib.no/ipq/). Illness identity was calculated by summing the positive (yes) response to the experience of symptoms attributed to ESRD. Responses on the illness perception subscales were scored accordingly (strongly disagree = 1, disagree = 2, neither agree nor disagree = 3, agree = 4, strongly agree = 5). Items IP1, IP4, IP8, IP15, IP17, IP18, IP19, IP23, IP24, IP25, IP26, IP27, IP36 required reverse scoring (1=5, 2=4, 4=2 and 5=1). The illness perception subscales were calculated by summing the following items:
Timeline (acute/chronic): sum items IP1 - IP5 + IP18
Consequences: sum items IP6 - IP11
Personal control: sum items IP12 - IP17
Treatment control items: sum items IP19 – IP23
Illness coherence items: sum items IP24 – IP28
Timeline cyclical: sum items IP29 – IP32
Emotional representations: sum items IP33 – IP38

In all the analysis to follow in sections of this thesis, the IPQ-R subscales were computed using the SPSS syntax described below:

RECODE ip1 ip4 ip8 ip15 ip17 ip18 ip19 ip23 ip24 ip25 ip26 ip27 ip36 (1=5) (2=4) (4=2) (5=1).
COMPUTE timeline = 6*MEAN.4(ip1,ip2,ip3,ip4,ip5,ip18).
COMPUTE timecycl = 4*MEAN.3(ip29,ip30,ip31,ip32).
COMPUTE conseque = 6*MEAN.4(ip6,ip7,ip8,ip9,ip10,ip11).
COMPUTE perscon = 6*MEAN.4(ip12,ip13,ip14,ip15,ip16,ip17).
COMPUTE treatcon = 5*MEAN.4(ip19,ip20,ip21,ip22,ip23).
COMPUTE illcoher = 5*MEAN.4(ip24,ip25,ip26,ip27,ip28).
COMPUTE emotrepr = 6*MEAN.4(ip33,ip34,ip35,ip36,ip37,ip38).
EXECUTE.

On subscales with 6 items Moss-Morris et al (2002) allowed for a maximum of 2 missing items (as evident by the .4 syntax command). For the remainder, 1 missing item per subscale was allowed (as evident by “.” number of items-1 syntax command).

4.5.4 The assessment of Depression
As described in chapter two assessing depression among physical illnesses is problematic largely due to the potential overlap between depression symptoms and those of somatic illness. Currently there is no accord as to how to best deal with somatic items in both diagnostic and screening methods. Furthermore screening tools lack diagnostic capabilities, instead providing an assessment of symptomatology in terms of frequency and severity.
However self-report methods have the advantage of practicality, allowing a large population to be assessed. On the negative side self-report methods like the BDI contain a number of somatic items that inflate estimates of depression prevalence when using conventional cut-off scores. Diagnostic schemes generally produce less false positive cases but are not best suited for research activities or for the regular clinical evaluation of a large population. It is important to be cognizant of the distinction between diagnoses and severity, as both assessments have different underlying assumptions yet both are often attributed the same term, “depression”. The term depression as applied to the results of subsequent chapters refers to a symptom severity and not a diagnosis.

In the empirical studies to follow, depression symptoms were assessed by a self-report severity measure, namely the BDI-II (Beck, Steer, & Brown, 1996). The BDI is a widely administered self-report questionnaire designed to assess the severity of depressive symptoms including cognitive, affective, and behavioural components. The BDI-II consists of 21 items, which are each rated upon a 4 point ordinal scale (0-3) indicating the frequency or severity of a particular depressive symptom (scores range from 0-63). The scores are summed to given a total depression score of which higher scores represent the reporting of more and severe symptoms. According to Beck et al (1996) a cut-off score of 13 indicates minimal depression, 14-19 mild depression, 20-28 moderate depression and ≥29 severe depression.

The BDI-II is a revision of the original BDI-1A in order to correspond with the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition (DSM-IV) criteria for Major Depressive Disorder. The BDI-II included four new items not present in the BDI-1A: Agitation, Worthlessness, Loss of Energy and Concentration Difficulty. Four items on the BDI-1A: Weight Loss, Body Image, Work Difficulty and Somatic Preoccupation, were not included in the BDI-II. In addition the BDI-II asks patients to answer the questions regarding how they have been feeling over the “past two weeks, including today”, reflecting the time-frame for symptoms described in the DSM-IV. The BDI-II has been found to have good reliability (α=0.91) in outpatients samples with various psychiatric disorders (Beck, Steer, Ball, & Ranieri, 1996). Comparison of the BDI-II with the BDI-1A reveals similar correlates with regards to sex, ethnicity, diagnosis of mood disorder and anxiety, however
it was found that the BDI-II total scores were approximately two points greater than the total scores of the BDI-1A (Beck, Steer, Ball et al., 1996).

The BDI-II was chosen for use in the studies to be presented because it conforms to current diagnostic criteria for MDD (DSM-IV), and because its properties in general and clinical samples have been well examined (Beck, Steer, & Brown, 1996; Steer, Ball, Ranieri, & Beck, 1999). Furthermore, the original BDI has also been used with the ESRD setting and more recent work has shown the original compares well with diagnostic standards, if cut-off scores are adjusted upwards (Grant et al., 2008). In one of the first empirical studies to test the BDI in ESRD patients Craven et al (1988) evaluated the measure against DSM-III criteria for depression in 99 patients. Craven et al (1988) found that a BDI ≥15 produce optimal sensitivity (0.92) and negative predictive value (0.99). The authors note that increasing the cut-off above ≥15 decreased sensitivity and did not produce a meaningful increase in positive predictive value.

More recent data confirms that the cut-off on the BDI needs to be adjusted upwards for use in ESRD patients, presumably due to increased somatic experiences encountered in this population. For example, a BDI cut-off ≥16 was shown to compare well with diagnostic standards, revealing a 91% sensitivity and 86% specificity for depression as assessed by the SCID in ESRD patients (Watnick et al., 2005). In addition, Watnick et al (2005) revealed utility for the shorter Patient Health Questionnaire (Spitzer, Kroenke, & Williams, 1999), where a cut-off score of ≥10 was associated with 92% specificity and sensitivity.

The BDI and CES-D measures were compared against the SCID in a larger study of 98 HD patients (Hedayati et al., 2006). The authors report that a CES-D score >18 gave 69% sensitivity and 83% specificity for depression. A BDI cut-off of 14 yielded 62% sensitivity and 81% specificity. A recent study in UK dialysis patients compared the BDI against the ICD-10 diagnostic criteria for MDD (Grant et al., 2008). Analysis of 57 dialysis patients BDI scores against the diagnostic criteria found that a BDI ≥15 produces 78% specificity and 100% sensitivity, whereas a BDI ≥20 produces 92% specificity and 71.4% sensitivity.

These studies have all utilised the BDI and compared them against diagnostic standards. Interestingly these studies have utilised the original BDI and not the BDI-II. Given that the
BDI-II leads to slightly higher mean total scores as compared to the BDI, it could be assumed that a cut-off score based upon the BDI-II in ESRD would be marginally higher than the 14-15 cut-off scores reported in studies that has used the BDI. However it should be noted that some confusion has been reported within the wider literature regarding the correct citation of versions of the BDI (Scalera & Shear, 2002). For example, in one ESRD study the authors failed to cite the version of the BDI used, instead citing apparent “validation” studies (Watnick et al., 2003). The failure to adequately describe the questionnaire version inhibits the reliable comparison of scores between studies (and estimated prevalence based upon cut-off scores which differ between versions) and may misinform as to which version to use in subsequent studies. In all the empirical works that follow the term BDI refers to the BDI-II.

4.6 The assessment of Extra Renal Comorbidity

Extra renal co-morbidities are common among individuals with ESRD and are associated with adverse clinical outcomes (Collins, Hanson, Umen, Kjellstrand, & Keshaviah, 1990). Accordingly some adjustment for this case-mix is desired particularly when evaluating prognostic models or conducting empirical analysis of the kind to be presented. Currently numerous co-morbidity scoring systems have been developed which differ in their approach and complexity. Methods that adopt a continuous measurement approach include the Charlson Index (Charlson, Pompei, Ales, & MacKenzie, 1987) and the ESRD-Severity Index (Craven, Littlefield, Rodin, & Murray, 1991). Stratification into risk groups is also popular (Chandna, Schulz, Lawrence, Greenwood, & Farrington, 1999; Davies, Phillips, Naish, & Russell, 2002; Khan et al., 1993; Wright, 1991). Currently there is no consensus as to which methods is preferred, while others suggest that the separate assessment of individual co-morbidities provides a better case mix adjustment (Van Manen et al., 2003).

Of the current semi-quantitative approaches the Davies method is the simplest. The rationale behind this approach was to define a simple index of co-morbidity that could define a group of patients at high risk of adverse clinical outcomes (Davies et al., 2002). Accordingly one point for each of the following conditions is assigned: ischemic heart disease (defined as prior myocardial infarction, angina, or ischemic changes on ECG), left ventricular dysfunction (defined as clinical evidence of pulmonary oedema not due to
errors in fluid balance, or history of congestive heart failure), peripheral vascular disease (includes distal aortic, lower extremity, and cerebrovascular disease), malignancy, diabetes, collagen vascular disease, and other significant pathology. The grade of co-morbidity is then derived from this total score; low (score=0), medium (score of 1-2) and high (score of 3 or more). The Davies method has been shown to compare well with the Charlson index, and predicts hospitalisation and death in ESRD patients (Fried, Bernardini, & Piraino, 2003), although its initial use and validation is restricted to the PD population.

The work to follow utilised the method described by Chandna et al (1999), a semi-quantitative approach not that dissimilar to the methods proposed by Davies et al (2002) and Wright (1991). This method was adopted in the work to follow for the following reasons; 1) data has shown that the present method has increased prognostic power compared to other semi-quantitative approaches (Chandna et al., 1999), 2) it incorporates severity into the coding and, 3) the clinicians responsible for the coding were involved in the development of the approach thus had valuable insight and familiarity with the concept. Patients were scored on the number and severity of the following conditions: Cardiac Disease, Peripheral Vascular Disease, Liver disease, Central Nervous System disorders, and Respiratory disease. Cardiac disease was rated according to the New York Heart Associations functional classification. The other disease groups were scored in a similar manner: 0= none, 1= minimal, 2= mild, 3= moderate and 4= advanced. Cancer was also graded (1-4) according to its activity and nature (medium term survival). Cirrhosis was scored as a 4. Scores were summed to form a combined co-morbidity score. To note, diabetes was not considered in the scoring system, rather treated as a separate condition. Patients were then stratified according to their score, following a similar classification to Wright (1991) and Davies et al (2002). A score of ≥3 was graded as “high” if the total score was derived from at least one illness group (i.e. at least moderate disease in one system). Medium risk was defined by a score of 2-3 (where a score of 3 was not derived from one system group). A score of 0-1 was defined as low risk.

4.7 Functional Status

The assessment of Functional Status is a useful complement to clinical and demographic information as a method of quantifying disease impact. The Karnofsky Performance Scale
(KPS) was developed in the cancer setting and is a widely used method of assessing functional status (Karnofsky, Abelmann, Craver, & Burchenal, 1948). The KPS consists of an 11 item ordinal scale (see table 4.3). A score of 100 represents normal functioning and, zero is death. In research the KPS is also treated by its functional classes with various categorisations employed (Joly et al., 2003; Zubrod et al., 1960), for example ≥70 to signify independent functioning. It is common for researchers to use both the ordinal scale and categorical function groups, and there is no consensus as to which method is preferable. Rather preference for either method should be judged according to the distribution of the data collected. Furthermore little work has been conducted within ESRD patients to examine the reliability of KPS. Early data suggests that the KPS has poor inter-rater reliability in HD patients (Hutchinson et al., 1979), however data from the oncology setting suggests a far higher inter-rater reliability (Schag, Heinrich, & Ganz, 1984).

The KPS has been extensively applied to the ESRD population (Edgell et al., 1996). Despite the lack of investigations pertaining to the psychometric properties of the KPS in ESRD, there is evidence that KPS scores predict adverse outcomes in ESRD. Several studies have shown that functional status as measured by the KPS predicts mortality in ESRD (Chandna et al., 1999; Ifudu, Paul, Homel, & Friedman, 1998; McClellan, Anson, Birkeli, & Tuttle, 1991) and acute renal failure (Perez Valdivieso, Bes-Rastrollo, Monedero, De Irala, & Lavilla, 2007). For example in a sample of incident dialysis patients McClellan et al (1991) reported that the KPS score was a significant independent predictor of mortality after controlling for several covariates including Quality of Life, age and co-morbidity.

4.8 Cognitive Function

Although in the work to follow cognitive function was not evaluated in relation to the psychology factors, it was necessary to screen for cognitive impairment using a screening method. The Mini Mental State Examination (MMSE, Folstein et al., 1975) was employed to ensure that the patients had adequate capacity to complete the questionnaire methods. The MMSE consists of 30 items evaluating various dimensions of cognitive ability including orientation, memory and arithmetic. A score of ≥25 from a possible 30 indicates “intact” functioning, although adjustments can be made for age. In the work that follows cognitive
Impairment was indicated by an age adjusted score of <22 on the MMSE (Folstein et al., 1975).

**Table 4.1: KPS classification**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>General Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal functioning</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>Normal Activity minor signs of disease</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>Activity with some effort minor signs of disease</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>Care for self but unable to carry on with normal activity</td>
<td>Dependent Activity</td>
</tr>
<tr>
<td>60</td>
<td>Requires some assistance, but cares for self</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent care</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Disabled. Requires considerable care</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Severely Disabled, hospitalisation indicated</td>
<td>Progressive deterioration</td>
</tr>
<tr>
<td>20</td>
<td>Very sick, Hospitalised, active support needed</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Moribund</td>
<td>Needs significant assistance</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
<td></td>
</tr>
</tbody>
</table>

4.9 Clinical Data

The following clinical data was collected for each of the studies presented in this thesis; Blood haemoglobin levels (Hb g/dL), dialysis adequacy (Kt/V_{urea}), serum albumin (g/dL) and serum C-Reactive-Protein (CRP mg/l). Dialysis vintage was computed (in days) for each patient from the time of dialysis initiation to the day of the study assessment. Primary renal diagnosis was coded in accordance with the data from the UK Renal Registry; Uncertain aetiology, Glomerulonephritis, Pyelonephritis, Diabetes, Polycystic Kidney, Hypertension, Renal Vascular Disease, Other. In addition smoking status was collected by self-report.

To determine whether patients had a *documented* history of depression, the problem lists from clinical letters and the electronic clinical data-bases were inspected. A positive depressive history was defined as having documented in the medical history either; “Depression,” “Major Depressive Disorder (MDD)” or “Manic Depression (Bi-Polar).” Transplant status was determined via self-report. Patients were asked if they were currently on the transplant waiting list (yes, no or don’t know). It was felt that the patient’s perception and knowledge regarding their transplant status would be more closely related
to their mood and illness perceptions, rather than their actual status. Other clinical methods pertaining to particular chapters are described in the relevant sections.

4.10 Demographic Information

Age, gender, ethnicity, marital-status and work-status were collected by a 14 item patient question (see appendix). Due to the small numbers of eligible patients from ethnic populations represented in the work that follows, patients were grouped as white vs. non-white. All categorical variables were dummy coded (i.e. male= 0 vs. female =1, white =0 vs. non-white) in the analyses that follow.

4.11 Statistical Software

All univariate and multivariate (excluding SEM) analysis was evaluated in SPSS v.17. All SEM and related analysis was evaluated in Mplus version 5.21 (Muthén & Muthén, 2007).

4.12 Statistical Analysis

The statistical analysis presented as a part of this thesis employed an array of statistical methods suited to the hypothesis under investigation and the suitability of the techniques given statistical assumptions and the consideration of sample size. Where relevant the statistical analyses that pertain to particular studies are described in the chapters that follow. The following section briefly describes some common features that apply to the majority of the data to be reported, and then focus more specifically on SEM and Latent Growth Models.

Univariate comparisons between groups were evaluated using t-tests, Mann-Whitney U test depending on the distribution, or in cases where three of more groups were compared Analysis of Variance (ANOVA). Differences between groups with respect to the distribution of categorical variables were examined using the Chi-squared test. In several chapters the illness perceptions of “depressed” and “non-depressed” patients were compared (chapter 7 & 8). Given that there were several illness perceptions to be compared between the depressed and non-depressed patients there was the potential for type I errors. A more appropriate analysis is Multivariate analysis of Variance (MANOVA). MANOVA allows the combination of several dependent variables - DVs (i.e. illness perceptions) into one analysis thus controlling type one error. In MANOVA a combined overall effect between the
categorical independent variable-IV (i.e. depressed vs. non-depressed) and the DVs (illness perceptions) is calculated. Furthermore differences between the groups with regards to individual DVs (illness perceptions- i.e. coherence) are evaluated. MANOVA also features in chapter 9 because comparisons of illness perceptions between “adherent” and “non-adherent” patients were sought.

Two of the chapters reported here employed logistic regression to predict a binary outcome, specifically depression (chapter 7) and adherence (chapter 9). Logistic regression differs from conventional linear regression in that the underlying function refers to probabilities (odds). Further, the assumption surrounding the normal distribution of IVs is less stringent. For this method variables were entered in a hierarchical manner in order to examine the improvement in the regression models after adding particular variables. In the first two steps demographic and clinical variables were evaluated as predictors of the outcome variable. In a final step illness perceptions were entered in order to evaluate their association with the outcomes variables after controlling for the demographic and clinical factors. A significant change in the chi-square (Δchi-square) between two models is interpreted as an improvement in the model fit. Nagelkerke R² was evaluated as a measure of explained variance in the dependent variables. In logistic regression the interpretation of the regression estimates are as odds ratios. That is, a 1 point increase (or decrease) in the IV increases (or decreases) the odds of the outcome variable (e.g. depression).

4.12.1 Structure Equation Modeling

The following sections on Structural Equation Modeling (SEM) attempt to provide a brief overview of the techniques employed at later points in this thesis. Specific details of the models tested including their specification are described in the relevant empirical chapters.

SEM is family of related statistical techniques that allows relationships between one or more independent (IV, exogenous) and dependent variables (DV, endogenous) to be evaluated. In SEM either the IV or DV can be measured directly (i.e. an absolute score) or as latent variable (a variable that is not directly measured but is assumed to be related to directly observable variables). A latent variable typically refers to some hypothetical construct that is not directly observable, examples of which could be personality, cognitive ability and depression. SEMs are often depicted graphically. Table 4.2 displays the common
symbols employed in SEM diagrams. An example SEM path model is shown in figure 4.2. The model shows three IVs and two DVs. The three IVs are specified to be intercorrelated as indicated by the double headed arrows between them. The single headed arrows between the IVs and DVs are stating a direct association between the two variables that is, the IV is predicting the DV. Statistical estimates of the direct effects are estimated in the modeling procedure which are interpreted as regression coefficients (either standarised or unstandardised). Inspection of figure 4.2 shows that DV1 is actually both an IV and DV, as not only do IVs 1-3 predict DV1, DV1 has a direct path form it to DV2. Specifying a model in this way allows tests for mediation, otherwise known as indirect effects.

Table 4.2: Symbols commonly used in SEM

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed variable- a variable directly observable by the researcher.</td>
</tr>
<tr>
<td></td>
<td>Latent variable- a variable that is unobserved (factor)</td>
</tr>
<tr>
<td></td>
<td>Direct effect between two variables i.e. X → Y: X is a predictor of Y</td>
</tr>
<tr>
<td></td>
<td>Correlation or covariance- two variables assumed to co-vary but no hypothesis about the direction is stated – “unanalysed association”</td>
</tr>
<tr>
<td>E</td>
<td>Residual Error- unexplained variance</td>
</tr>
</tbody>
</table>
In the model of figure 4.2 IVs 1-3 are set to predict DV1 and DV2. Furthermore, indirect effects of IVs 1-3 on DV2 through (as mediated by) DV1 is also specified in the model. Of course instead of observed variables latent variables could be included in the model.

There are a number of advantages to employing SEM techniques over conventional regression analysis. Firstly in SEM multiple DVs can be assessed in the models, and latent variables can be included in the specified model. Moreover SEM allows a cleaner statistical model as it estimates the residual variance (the error) and accounts for this “error” in the modelling. For these reasons SEM was utilised in chapter 8 particularly as there were multiple DVs to model (illness perceptions) and meditational effects (indirect relationships) to evaluate. Moreover illness perceptions could be treated as latent variables and their relationship with depression modelled after accounting for measurement error.

4.12.2 Model Estimation and Fit

Model estimation techniques determine the model parameters (as in regression analysis). Maximum likelihood (ML) is the most common estimation method and allows all parameters to be simultaneous estimated. The mathematical operations of ML estimation are far beyond the scope of this chapter. In brief, ML estimation assumes the estimates to be population values, which are the values that maximise the likelihood that the data (observed covariances) were drawn from this population.
Another estimation technique is Weighted Least-Squares with Mean and Variance Adjustment (WLSMV) estimation. WLSMV was employed in the SEM models that follow (excluding the latent growth models) because it is an appropriate technique when the data is skewed, categorical or ordinal. The WLSMV estimation unlike Maximum Likelihood (ML) procedures makes no assumptions about the distribution of the data (Muthén & Muthén, 2007) and models polychoric correlations. WLSMV estimation has been shown to produce accurate model statistics across models that vary in sample size, complexity and normality (Flora & Curran, 2004).

The essential question in SEM is whether the observed covariance matrix from the sample data fits, or is similar to, the estimated covariance matrix (i.e. the proposed model). In other words does the model derived data fit with the actual sample data. Typically this can be evaluated using a chi-square goodness of fit test, which derives the deviation between the estimated covariance matrix with the observed covariance matrix. A non-significant chi-square is desired suggesting that the reproduced and observed covariance matrixes do not differ significantly hence the data fits the proposed model structure. However the chi-square statistic is very sensitive to sample size (Ullman, 2006), and it is quite often the case that the chi-square is significant. For these reasons fit indices are utilised in conjunction with the chi-square test to inform the relative fitness of a model. The comparative fit index (CFI) is an incremental fit index that compares the proposed model with the null model, and uses an approach based on the noncentral chi-square distribution (Bentler, 1990). A CFI $\geq 0.95$ indicates good fit (Hu & Bentler, 1999). The Tucker Lewis Index (TLI) was also employed, which has the a similar interpretation to the CFI but also considers the number of parameters (Tucker & Lewis, 1973). A final index, The Root Mean Square Error of Approximation (RMSEA) considers model complexity. A RMSEA $<0.05$ is considered to demonstrate reasonable fit, while a value of $>0.1$ suggests poor fit (Browne & Cudeck, 1993). All three indices were considered in the models that follow.

**4.12.3 Confirmatory Factor analysis (CFA)**

CFAs are known as measurement models in that they describe how observed variables (indicators) measure underlying concepts (latent factor). CFA is employed to test how well the latent factors explain observed variables (i.e. how well the model fits the data). CFA
differs from exploratory factor analysis because in CFA the researcher has an idea of the
proposed measurement structure and seeks to confirm the structure using SEM based
techniques. Consider the measurement model in figure 4.3, which specifies a two factor
measurement model.

![Figure 4.3](image)

**Figure 4.3:** An example of a CFA measurement model.

The latent variables (F1 & F2) are hypothesized to predict 3 observed items each (thus the
latent variables are in fact IVs). As an example, the latent variables here could be cognitive
(F1) and somatic (F2) items on a questionnaire, with the observed items representing the
scores for each particular question. Typically the latent variables are set to be correlated
(unanalyzed association). Each item also has corresponding error terms (E) that represents
the variance in the item that is not explained by the latent variable. Model fit is determined
by the methods described above. As with other SEM there is an opportunity to modify the
model according to modification indices computed by modeling software such as Mplus.
Model Modification uses modification indices to examine whether freeing parameters (an
effect between two variables) that are constrained to zero improves the model fit.
Furthermore, they can identify which parameters should be added to the model to improve
the model fit (Ullman, 2006), including the correlation of residual errors. Modification
indices estimate the amount by which the chi-square fit statistic will decline (i.e. improve)
when the modification is made. Modification can however be a dangerous procedure, as it
essentially turns the confirmatory technique into an exploratory one. It should be borne in
mind that the CFA is theory dependent so modification was only attempted if the proposed changes appeared theoretically valid. CFA of the BDI is presented in chapter 6 in order to evaluate the underlying structure of the questionnaire as applied to dialysis patients. In addition a CFA of illness perceptions as measured by the IPQ-R was evaluated in chapter 8.

4.12.4 Latent Growth Models

Latent growth models (LGM) are kinds of SEM for the analysis of longitudinal data and allow the trajectory of a measure (i.e. depression) to be assessed over time. Unlike alternative methods, LGMs account for residual variance for an observed item. Furthermore LGMs are particularly suited for longitudinal studies were patient attrition is expected as each individual trajectory is considered with all the available data. For these reasons LGMs were utilised in the longitudinal study presented in chapter 8, allowing the trajectory of depression over time to be evaluated.

In order to conduct LGM several requirements are necessary; 1) minimum of three time points, 2) dependent variables have the same units over time and measure the same construct, 3) data are time structured in that all are collected at the same intervals. Depicted in figure 4.4 is a LGM. As with all LGMs the dependent variables at each time point (V1-V3) are specified to be predicted by two latent constructs representing the intercept (starting value) and a slope (change over time). The intercept is analogous to the intercept on a regression equation (i.e. start value). All the loadings on this factor to each of the observed DVs are fixed to one. Since all three values are fixed at the same value, this is the constant level of depression, if there were no growth. The loadings on the slope are fixed at intervals of 0, 0.5 and 1 which represent the times of the measurement (i.e. at baseline, half a year and 1 year). In this example the rate of change is specified as linear because the time slopes are increasing by the same amount at every interval. Finally the intercept and slope are said to co-vary, that is the estimate of this covariance indicates whether the initial level is related to change over time. Unspecified growth models allow one or more (in larger models) of the slope estimates to be freely estimated by the statistical software. Such models are often employed when the function of the change over time is not known (non-linear). In addition LGMs can also be included as a part of SEMs. For example, factors that are thought to predict the slope or intercept can be entered by
regressing the latent variables (slope and intercept) onto the hypothesised predictors (illness perceptions). This kind of modelling features in chapter 8 where illness perceptions are specified to predict the slope (i.e. change) of depression.

![Figure 4.4: An example of a latent growth model.](image)

4.13 General Comments

A description of the general methodologies employed in the works throughout this thesis has been described, including the measurement of depression and illness representations and the assessment of co-morbidity. Moreover an overview of the study designs and statistical methods have been presented.

The following chapter presents a pilot study that examined the application of the methods. Specifically, the validity and reliability of assessing depression and illness perceptions while on-dialysis is evaluated.
Chapter 5

Screening for depression and assessing illness perceptions: An evaluation of on-dialysis assessment

5.1 Introduction

This chapter serves to evaluate the application of the questionnaire methods (BDI and IPQ-R) which are employed throughout this thesis. The intention was to establish whether the BDI and IPQ-R questionnaires could be completed while patients were actively on HD. On-dialysis assessment has some particular advantages for research and clinical based activities, particularly as the vast majority of patients reported in this programme of empirical work were receiving in-hospital HD. Indeed, on-dialysis assessment attempts to standardise the condition in which patients are assessed, while also being highly practical. From a clinical perspective assessing depression symptoms while patients dialyse may provide a platform for regular assessment in this setting. The work of James W. Pennebaker (1982) on the “Psychology of Physical Symptoms” is also relevant in this chapter as the context of dialysis may lead to a variety of sensory and perceptual experience which could influence self-reported symptoms. This chapter serves to evaluate the application of the methods, and not to explicitly test theories relating to symptom perception. However pragmatically, the work here allowed comment on these theories as an additional interest.

A pilot study is presented, in which on-dialysis assessment of depression symptoms (BDI) and illness perceptions (IPQ-R) were compared with the same measures completed off-dialysis. In addition to evaluating the context of assessment, the accuracy of the BDI as compared to diagnostic criteria for MDD was also assessed.

5.1.1 Screening for depression in HD patients

As discussed previously, the numerous methods employed to assess depression or depressive symptoms contribute to the variation in reported prevalence estimates. Further, there remains substantial debate regarding the most effective way to assess and define

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4 To note, parts of this chapter have been published in; Chilcot, J., Wellsted, D., Farrington, K (2008). Screening for depression while patients dialyse: an evaluation. *Nephrology Dialysis & Transplantation, 23*(8):2653-9
depression among illness states, with reference to both screening and diagnostic methods. Owing to the lack of clear direction in this debate I have decided to focus predominantly on the application of a depression screening tool (BDI) in this chapter. The logic here was to establish a procedure which could fulfil the needs of subsequent works which investigated depression symptoms and illness representations in longitudinal and cross-sectional samples of ESRD patients.

Despite several published studies revealing the relative accuracy of the BDI as a screening tool among ESRD patients, the screening procedure has received sparse attention. In comparison with diagnostic interviews it is recognised that depression screening offers a practical solution that allows a large clinical population to be assessed. In an early review of the topic it was indicated that self-report depression tools may aid the detection and treatment of depression in medical settings (Meakin, 1992). However, the effectiveness of depression screening in clinical practice is questionable (Gilbody, House, & Sheldon, 2001a; Gilbody, Sheldon, & House, 2008). It is worth reiterating though that most of this data has been generated from primary care settings therefore the utility of depression screening among individuals with chronic illness is unknown. Screening techniques are unlikely to be of value unless they are routinely used and demonstrate an effect upon treatment prescription (Gilbody et al., 2001a). However screening is advocated if the costs are reasonable and the subsequent treatment options defined and available (Valenstein, Vijan, Zeber, Boehm, & Buttar, 2001). The scope of this chapter allows us to explore the procedure of regular depression assessment in ESRD patients in order to promote both a research and a clinical method.

It seems reasonable to regularly assess mood in ESRD patients given that depression is prevalent and associated with adverse outcomes. It is suggested here that that on-dialysis screening is one possible technique that would satisfy this need. Drayer et al (2006) reported assessing depression while HD patients were dialysing, in an attempt to minimize the impact of fluctuating uraemic symptoms on mood and cognition that would inevitably be present in patients during the interdialytic period (Drayer et al., 2006; Kurella, Chertow, Luan, & Yaffe, 2004). However, few studies have explicitly employed on-dialysis assessment and little is known about the legitimacy of such a procedure. The uncertainty here is whether the context of actively dialysing influences depression screening? The purpose of
the work reported is to evaluate the reliability of on-dialysis assessment. Specifically we investigated the level of agreement (LoA) between BDI scores obtained on-dialysis with scores obtained off-dialysis. Level of agreement (Bland & Altman, 1986) is appropriate in this context as we anticipated some intra-individual variation in symptom reports over a period of time. We were particularly interested in understanding if on-dialysis assessment had a substantial influence on somatic BDI scoring.

The focus of this pilot work was extended in order to examine the accuracy of the BDI in relation to a diagnostic standard for MDD. This was deemed to be of importance because at the time of this study all related data originated from the United States, thus no comparable UK data was available. Examining the accuracy of the BDI allowed us to determine a BDI cut-off score relevant to our sample of haemodialysis patients.

5.1.2 Does the context of dialysing influence self reported illness perceptions?

The second question addressed in this chapter concerns the viability of on-dialysis IPQ-R assessment. The primary aim here was to define the level of agreement between subscale scores on the IPQ-R, completed on- and off-dialysis.

Previous research has shown that the interpretation of symptoms is dependent upon a range of factors including mood, cognition and environmental factors. The seminal work of James Pennebaker revealed that individual perceptions of symptoms often correlate poorly with physiological states (Pennebaker, 1982; Pennebaker & Watson, 1988). Indeed, perceptual experiences can be influenced by cognitive schemata which influence the selective search, and inference of symptoms and sensations (Pennebaker, 1982; Skelton & Croyle, 1991). Pennebaker (1982) demonstrated the importance of attention on symptom perception. It was proposed that because attention is finite, internal sensory and external stimuli compete for attention. According to Pennebaker (1982) “the probability of noticing internal cues can be expressed as a function of the ratio of the quantity or salience of potential internal information to external information” (p.21). Therefore if the environment is of sufficient interest to the individual, attention will be directed towards the particular external stimuli resulting in the decreased selection of encoded internal sensations. Similarly if the environment is boring or tedious, internal sensory processes are likely to be selected after encoding (i.e. active in working memory) as attention would be directed
inwards. For example in a novel study, Pennebaker (1982) found a significant negative correlation between reported interest in an environmental stimulus (video) and the attention paid to internal states, as measured by the number of coughs recorded during the video viewing. Pennebaker argued that the lack of environmental interest directed attention inwards so that every tickle in the throat and chest was more salient to the individual. While the validity of this approach is questionable Pennebaker and colleagues demonstrated similar effects across various paradigms, including the perception of heart palpitations. Other reports have demonstrated support for the competition of cues principle regarding the perception of fatigue (Fillingim & Fine, 1986), and have shown that the manipulation of self-focused attention increases symptom reports (Pennebaker, 1982; Schmidt, Wolfs-Takens, Oosterlaan, & van den Hout, 1994).

The importance of symptom perception is highly relevant in this context since symptoms form an integral part of an individual’s illness representation. As described earlier the bi-level nature of illness representations (abstract vs. concrete levels) can activate cognitive and emotional representations of disease (Leventhal et al., 1980). The context of dialysis does induce physiological changes resulting in a variety of physical sensations. In addition given that routine dialysis treatment is somewhat tedious, sensory perceptions may be influenced according to the competition of cues principle (Pennebaker, 1982). Put another way, the environmental context of dialysis could impact symptom perception due to an internal attentional focus, which may then alter reported illness perceptions. In order to observe whether illness perceptions differed across assessment conditions, we compared IPQ-R perceptions reported on-dialysis with off-dialysis assessments. To further evaluate the impact of contextual factors upon self-reported physical symptoms, we also analysed the number of endorsed physical symptoms patients reported having since their kidney problem (taken from the IPQ-R identity scale), regardless of whether they attributed the symptom to ESRD.

While focus of attention can influence symptom reports, there is also evidence that negative affect and self-focused attention are associated (Duval & Wicklund, 1972; Pyszczynski & Greenberg, 1987; Salovey, 1992). Indeed it is thought that negative affect draws attention to somatic symptoms (Stegen, Van Diest, Van de Woestijne, & Van den Bergh, 2001). For example experimentally induced negative mood has been shown to
heighten self-focus and influence perceptions of perceived health and symptoms reports (Croyle & Uretsky, 1987). Of further empirical interest is the potential “joint-impact” between mood and self-focused attention upon reported symptoms (Gendolla, Abele, Andrei, Spurk, & Richter, 2005). The potential interaction between depression and assessment condition (on- vs. off-dialysis) upon the number of self-report symptoms was explored in sub-analysis.

In summary, the main aims of the pilot work here were as follows:

**Primary aims:**

1. To test whether depression symptoms and illness perceptions varied across the assessment conditions (on- vs. off-dialysis).

**Secondary aims:**

2. To examine the accuracy of the BDI against a diagnostic standard for MDD.

3. To test whether there was any interaction between the assessment condition (on- vs. off-dialysis) and depression (depressed yes vs. no) upon reported illness perceptions.

### 5.2.1 Methods

### 5.2.2 Participants

HD patients from the renal service of the East and North Hertfordshire NHS Trust were approached, excluding patients with known dementia or a history of major psychiatric disorders other than depression. Adult ESRD patients who had been receiving HD for >3 months were recruited. All patients were receiving high-flux haemodialysis or on-line haemodiafiltration three times weekly. None of the patients required hospitalisation between assessments.

Forty-three adult HD patients agreed to participate, corresponding to a 78% consent rate. Two patients dropped out of the study prior to follow-up, and one patient was excluded due to a significant counselling intervention being provided between assessments.
5.2.3 Materials

The BDI, IPQ-R and MMSE have been described previously. To note, the IPQ-R causal perceptions were not included in the analysis in this particular study. As an addition, the number of endorsed physical symptoms from the initial part of the illness identity scale (IPQ-R) was summed, regardless of whether the patient believed the symptom was due to ESRD. This symptom inventory allowed the comparison of the number of reported physical symptoms across conditions. A 15 item non-somatic subscale of the BDI (cognitive depression index – CDI), was computed according to the work of others (Sacks et al., 1990). The rationale of the CDI according to Sacks et al (1990) is to remove the potential problematic somatic questions leaving a cognitive subscale. As discussed previously this specific approach has not been subject to factor analysis in the ESRD population. This issue is addressed further in the following chapter which evaluates the factor structure of the BDI-II. However at this point there was insufficient data to conduct a factor analysis in order to understand the particular structure of the BDI (i.e. cognitive and somatic). Rather given its use within the renal literature, and because comparing cognitive and somatic symptoms separately is desired here, the CDI subscale was used in the form described elsewhere (Sacks et al., 1990).

Depression was assessed using the Mini International Neuropsychiatry Interview (M.I.N.I). The M.I.N.I is a structured diagnostic interview for both DSM-IV and ICD-10 psychiatric disorders (Lecrubier et al., 1997; Sheehan et al., 1997). The M.I.N.I depression module consists of two diagnostic filter questions, concerning depressed mood and loss of interest during the past two weeks. If either of these symptoms is confirmed, seven additional symptoms are evaluated. These are; 1) loss of appetite, 2) sleeping difficulties, 3) restlessness, or slow movement or speech, 4) a lack of energy 5) feelings of worthlessness or guilt, 6) concentration difficulties, and 7) consideration of suicide or self-harming. The presence of five or more symptoms indicated MDD. The M.I.N.I has demonstrated high reliability and validity against the Structured Clinical Interview for Depression (SCID) and the Composite International diagnostic Interview (CIDI) for MDD, data from which is
summarised in table 5.1 (Lecrubier et al., 1997; Sheehan et al., 1997). Sheehan et al (1997) report high inter-rater (kappa=1) and re-test reliability (kappa=0.87) for the M.I.N.I.

**Table 5.1:** Validity of the M.I.N.I against the SCID and CIDI.

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Study</th>
<th>N</th>
<th>Kappa</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCID</td>
<td>Sheehan et al (1997)</td>
<td>370</td>
<td>0.84</td>
<td>0.96</td>
<td>0.88</td>
<td>0.97</td>
<td>0.93</td>
</tr>
<tr>
<td>CIDI</td>
<td>Lecrubier et al (1997)</td>
<td>343</td>
<td>0.73</td>
<td>0.94</td>
<td>0.79</td>
<td>0.56</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*N: sample size. PPV: Positive Predictive Value. NPV: Negative Predictive Value*

### 5.2.4 Demographic and Clinical data

Demographic characteristics as described in the general methods, accompanied by routine clinical parameters (haemoglobin, albumin and Kt/V) were collected. In addition, whether patients were on anti-hypertensive medication was recorded from medical notes. Co-morbidity was defined using the methods described in chapter 4 (Chandna et al., 1999).

### 5.2.5 Design and Procedure

The study employed a within-subjects design, with the order of assessments counterbalanced to control for order effects. Assessment order was randomised determined by a random number sequence, with the order allocated on the basis of the next available order as the patients were recruited. Patients were asked to complete the BDI, IPQ-R and demographic questionnaires during a stable dialysis session, commencing 30 minutes after initiation.

The off-dialysis assessments were completed either before or after a treatment session according to patient preference. For the off-dialysis assessment patients were invited to the renal unit to complete the same questionnaires (BDI and IPQ-R), with the addition of the interview component involving the M.I.N.I and MMSE. The on- and off-dialysis assessments took place on average 10.7 (±4.2) days apart.

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*A kappa=1 suggests perfect concordance between raters, thus caution should be noted here as one would expect some discrepancy in a sample of 370.*
5.2.6 Analysis

The primary aim was to determine the extent to which the situation in which patients were assessed (on dialysis or not) influenced their response. The default assumption was that the situation would have no discernable influence on the patients’ responses. A high level of agreement (LoA) was therefore expected between the two BDI assessment scores and the two sets of illness perception data (on- vs. off-dialysis). Level of agreement was assessed by the method described by Bland and Altman (1986). A high level of agreement would indicate that the location of the assessment did not influence the patient’s responses to the assessment tool. Furthermore given that up to this point there is no data concerning the internal reliability of the IPQ-R dimensions in dialysis patients, Cronbach’s α were calculated for IPQ-R scores on- and off-dialysis.

Receiver Operating Characteristic (ROC) analysis was used to determine suitable cut-offs for the BDI and CDI, measured against the diagnostic scheme. Chi-Square tests were employed to test associations between the diagnostic scheme, and defined BDI and CDI cut-offs.

Interactions between depression (assessed by the M.I.N.I) and the assessment condition upon reported illness perceptions were evaluated in mixed model ANOVAs, with one between subjects variable (depressed yes and no) and one within subjects variable (assessed on- and off-dialysis). Main effects of depression and the assessment condition upon illness perceptions were evaluated accompanied by their interaction (i.e. depression*assessment).
5.3 Results Part I: The assessment of depression on-dialysis

The following results section is structured in two parts; (1) compares on- and off-dialysis BDI assessments, and evaluates the accuracy of the BDI against the M.I.N.I and, (2) compares the IPQ-R responses assessed on- and off-dialysis. In addition the interaction between depression and the assessment condition upon reported illness perceptions was evaluated.

5.3.1 Patient characteristics

Patient characteristics and clinical data are displayed in table 5.2. Of the forty patients assessed, 22.5% (n=9) met the criteria for MDD based upon the M.I.N.I. Comparisons were sought between the depressed and non-depressed with regards to demographic and clinical factors. As observed in table 5.2 there were no significant demographic or clinical differences between the groups, although haemoglobin did near significance.

5.3.2 On- vs. off-dialysis BDI assessment

Table 5.3 displays the mean BDI and CDI scores on- and off-dialysis, for the whole sample and for subsets defined by the presence of depression based upon the diagnostic assessment. For depressed patients, the mean BDI and CDI scores did not differ significantly across the assessment conditions. However the non-depressed scored significantly higher on the somatic component of the BDI while on-dialysis, evident by significantly higher BDI scores but similar CDI scores. Across all patients this effect was maintained (Cohen’s effect size, d =0.41). LoA plots for the BDI and CDI are displayed in figure 5.1. The mean difference between the BDI scores on- and off-dialysis was 1.8 (±4.29) indicating a non-significant bias for higher scores on dialysis, and the 95% confidence range of agreement was -6.8 to +10.4. Similarly the mean difference between CDI scores was 0.95 (±3.26) biased to on dialysis with a confidence range of -5.6 to +7.5 (non-significant). Both LoA plots depict satisfactory levels of agreement across the two conditions.
Table 5.2: Demographic and clinical data: comparing depressed and non-depressed patients.

<table>
<thead>
<tr>
<th></th>
<th>N=40</th>
<th>Depressed (n=9)</th>
<th>Non-Depressed (n=31)</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender % (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60 (24)</td>
<td>44.4 (4)</td>
<td>64.5 (20)</td>
<td>0.242a</td>
</tr>
<tr>
<td>Female</td>
<td>40 (16)</td>
<td>55.6 (5)</td>
<td>35.5 (11)</td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>55.0 (22.25)</td>
<td>46.0 (38.0)</td>
<td>59.0 (22.0)</td>
<td>0.463b</td>
</tr>
<tr>
<td>Ethnicity % (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>87.5 (35)</td>
<td>88.9 (8)</td>
<td>87.1 (27)</td>
<td>0.689a</td>
</tr>
<tr>
<td>Non-white</td>
<td>12.5 (5)</td>
<td>11.1 (1)</td>
<td>12.9 (4)</td>
<td></td>
</tr>
<tr>
<td>Work % (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50 (20)</td>
<td>44.5 (4)</td>
<td>51.6 (16)</td>
<td>0.809a</td>
</tr>
<tr>
<td>No</td>
<td>17.5 (7)</td>
<td>22.2 (2)</td>
<td>16.1 (5)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>32.5 (13)</td>
<td>33.3 (3)</td>
<td>32.3 (10)</td>
<td></td>
</tr>
<tr>
<td>Marital Status %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/Living with partner</td>
<td>72.5 (29)</td>
<td>88.9 (8)</td>
<td>67.7 (21)</td>
<td>0.195a</td>
</tr>
<tr>
<td>Divorced/Separated</td>
<td>15 (6)</td>
<td>11.1 (1)</td>
<td>16.1 (5)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>2.5 (1)</td>
<td>0 (0)</td>
<td>3.3 (1)</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>10 (4)</td>
<td>0 (0)</td>
<td>12.9 (4)</td>
<td></td>
</tr>
<tr>
<td>Dialysis Vintage (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>33.0 (51.0)</td>
<td>31.0 (63.5)</td>
<td>33.0 (52.0)</td>
<td>0.973b</td>
</tr>
<tr>
<td>Clinical Variables (mean ±SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>11.7 (±1.3)</td>
<td>10.6 (±1.9)</td>
<td>12.0 (±0.9)</td>
<td>0.065c</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>37.7 (±3.6)</td>
<td>36.5 (±3.7)</td>
<td>38.0 (±3.6)</td>
<td>0.296c</td>
</tr>
<tr>
<td>Dialysis Adequacy (Kt/V)</td>
<td>1.3 (±0.2)</td>
<td>1.3 (±0.2)</td>
<td>1.3 (±0.2)</td>
<td>0.231c</td>
</tr>
<tr>
<td>Active on Transplant List %</td>
<td>60 (24)</td>
<td>33.3 (3)</td>
<td>41.9 (13)</td>
<td>0.647a</td>
</tr>
<tr>
<td>Hypertensive medication %</td>
<td>70 (28)</td>
<td>77.8 (7)</td>
<td>67.7 (21)</td>
<td>0.568a</td>
</tr>
<tr>
<td>Extra-Renal Co-Morbidity %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None-Low</td>
<td>40 (16)</td>
<td>44.4 (4)</td>
<td>38.7 (12)</td>
<td>0.549a</td>
</tr>
<tr>
<td>Medium</td>
<td>40 (16)</td>
<td>44.4 (4)</td>
<td>38.7 (12)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>20 (8)</td>
<td>11.2 (1)</td>
<td>22.6 (7)</td>
<td></td>
</tr>
</tbody>
</table>

a Fisher’s Exact test b Mann-Whitney U c T-test IQR= inter-quartile range.
Figure 5.1: The level of agreement between the BDI (A) and CDI (B) assessments made on and off dialysis. Shown are the mean bias (middle line) and the limits of agreement (mean ±2SD), between which the vast majority of points lie.
5.3.3 Accuracy of the BDI and CDI

In order to assess the accuracy of the BDI in our sample of patients, off-dialysis scores were compared with the M.I.N.I. ROC analysis (see figure 5.2) showed high predictive accuracy for the BDI (area under the curve 0.961, p=0.001) versus the M.I.N.I. Optimal cut-off values were determined by the location in which the number of accumulating false positive values exceeded the number of false-negatives. The optimal cut-off detected for the BDI was ≥16. Employing this cut-off revealed an 88.8% positive predictive value, and an 87.0% negative predictive value, with 88.9% sensitivity (95% CI 75.1 to 95.5) and 87.1% specificity (95% CI 72.9 to 94.4). Chi-square analysis revealed significant associations between the M.I.N.I (depressed/non-depressed) and BDI classification ≥ 16 (Fisher’s exact test p=0.001, table 5.4). The mean BDI score for patients who did not meet the M.I.N.I criteria for depression but had a BDI ≥16 (discrepant cases) was 17.7 (range =3), compared to 25.7 (range=20) for those meeting both the M.I.N.I and BDI criteria. This difference was significant t(10)=2.4, p=0.03.

Figure 5.2: ROC curve for the sensitivity and specificity of the BDI.
Table 5.3: Mean BDI and CDI scores for patients assessed on and off dialysis, defined by those who meet the diagnostic criteria for MDD using the M.I.N.I.

<table>
<thead>
<tr>
<th>Depressed (M.I.N.I)</th>
<th>Measure</th>
<th>Dialysis</th>
<th>Not Dialysis</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>BDI</td>
<td>25.6 (7.0)</td>
<td>24.3 (7.4)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>CDI</td>
<td>16.2 (6.6)</td>
<td>15.0 (5.9)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Somatic</td>
<td>9.4 (2.1)</td>
<td>9.3 (2.5)</td>
<td>ns</td>
</tr>
<tr>
<td>No</td>
<td>BDI</td>
<td>9.3 (6.2)</td>
<td>7.3 (5.7)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>CDI</td>
<td>4.9 (4.2)</td>
<td>4.0 (3.9)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Somatic</td>
<td>4.4 (2.5)</td>
<td>3.3 (2.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total n=40</td>
<td>BDI</td>
<td>12.9 (9.3)</td>
<td>11.1 (9.4)</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>CDI</td>
<td>7.4 (6.7)</td>
<td>6.5 (6.4)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Somatic</td>
<td>5.5 (3.2)</td>
<td>4.7 (3.4)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Mean and Standard Deviation ~T-test

The analysis was replicated using the off-dialysis CDI assessment. ROC analysis revealed high predictive accuracy for the CDI (area under curve 0.941, p=0.001). The optimal cut-off detected for the CDI was ≥10. Employing a CDI≥10 led to 77.8% sensitivity (95% CI 62.3 to 88.1) and 80.6% specificity (95% CI 65.4 to 90.1) with 77.7% positive predictive value, 80.6% negative predictive value. These findings suggest that the CDI, excluding somatic enquiry, has reduced sensitivity and specificity compared to the BDI. Further, as compared to the M.I.N.I, using a BDI≥16 yielded 4 false positives and 1 false negative; whereas a CDI ≥10 had 6 false positives and 2 false negatives (table 5.4).

Table 5.4: False-Positive and False Negatives cases for the BDI and CDI against the diagnostic standard (M.I.N.I).

<table>
<thead>
<tr>
<th>M.I.N.I Depressed</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>8</td>
<td>4</td>
<td>12</td>
<td>7</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>BDI ≥16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>27</td>
<td>28</td>
<td>CDI ≥10</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>31</td>
<td>40</td>
<td>9</td>
<td>31</td>
<td>40</td>
</tr>
</tbody>
</table>

All numbers represent n cases
5.3.4 BDI and CDI cut-off classification on- and off-dialysis

When assessed on-dialysis 32.5% of patients had a BDI score ≥16 compared to 30.0% assessed off-dialysis. The CDI assessment was consistent across the conditions with 32.5% of patients scoring ≥10 in both conditions. Fisher’s exact test confirmed that there was a significant association between the number of patients who satisfied the BDI cut-offs (≥16) on- and off-dialysis (p=0.001, table 5.5).

Table 5.5: Comparison of patients classified as having significant depressive symptoms on and off-dialysis.

<table>
<thead>
<tr>
<th></th>
<th>Off-Dialysis</th>
<th></th>
<th>Off-Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI ≥16</td>
<td>Yes</td>
<td>No</td>
<td>CDI ≥10</td>
</tr>
<tr>
<td>On-Dialysis</td>
<td>11</td>
<td>2</td>
<td>On-Dialysis</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>26</td>
<td>No</td>
</tr>
</tbody>
</table>

*All numbers represent n cases*

5.3.5 Timing of the off-dialysis BDI and M.I.N.I assessment

The off-dialysis BDI and M.I.N.I assessments were timed according to patient convenience. Twenty-three patients conducted their off-dialysis assessment before a treatment session, and seventeen after. In order to determine if the timing of the off-dialysis assessment influenced the findings, patients who were assessed pre- and post-dialysis were compared. The number of patients who satisfied the M.I.N.I criterion when assessed before dialysis was 4, compared to 5 when assessed after dialysis. This difference was non-significant (Fisher’s exact test p=0.456).

The median off-dialysis BDI score, when completed before dialysis was 8.0 (inter-quartile range=10.0) compared to 5.0 (inter-quartile range= 17.0) after dialysis. This difference was non-significant (Mann-Whitney U = 192, p=0.94) suggesting that the timing of the off-dialysis assessment had no influence upon the BDI scores. As no differences were apparent, it is suggested that the above findings were not influenced by the timing of off-dialysis assessments (pre/post dialysis).
5.4 Conclusion I (Depression Assessment on- vs. off-dialysis)

The purpose of this section of the chapter was to ascertain the legitimacy of on-dialysis depression screening using the BDI. To summarise, on-dialysis screening appears viable, comparing suitably with off-dialysis assessment. From a practical stance on-dialysis depression screening is highly convenient for both research and clinical needs. Indeed, given the under recognition of depression in ESRD evident from the literature, screening for depression while patients dialyse may promote increased monitoring and recognition. In addition on-dialysis as compared to off-dialysis assessments yielded two more properties, (1) a small bias for increased on-dialysis scoring suggests that the BDI will capture more cases of depression and although increasing false positives will reduce false negatives, and 2) clinical interviews cannot be conducted on-dialysis, limiting the identification of depression. Taken together, this suggests a regimen of on-dialysis screening supplemented with diagnostic interviews for those patients identified as being at risk.

There was good agreement between on- and off-dialysis BDI assessments, as determined by LoA plots. Importantly these findings were not influenced by the timing of the off-dialysis assessment. On-dialysis assessment revealed significantly higher BDI somatic scoring, compared with the off-dialysis scores. While statistically significant, the practical implications of such a difference are relatively small. Critically the BDI and CDI scores did not reliably differ across the assessment conditions for patients who met the M.I.N.I criteria for MDD. Evidently the assessment condition did not influence the screening response for depressed individuals. The non-depressed scored consistently on the CDI but differed on the BDI, scoring reliably higher while dialysing. The heightened BDI scores reflected increased somatic scoring while dialysing. This effect was maintained across all patients. This could reflect the natural variation of symptoms (and perceived symptoms) over the assessment period or biased somatic scoring while on-dialysis. Given these findings it is suggested that on-dialysis assessment increases somatic not cognitive scoring rather than the suggestion that on-dialysis assessment may control the impact of fluctuating uraemic symptoms upon mood and cognition (Drayer et al., 2006; Kurella et al., 2004). Of course what may be meant here is that while on patients may be experiencing similar symptoms rather than fluctuating sensations possibly experienced over the interdialytic period.
Further, a BDI≥16 demonstrated good diagnostic accuracy for MDD as compared with a short clinical interview, supporting previous findings (Watnick et al., 2005) albeit it with the original BDI. In addition the BDI (≥16) inclusive of all somatic enquiries, had increased sensitivity and specificity over the CDI (≥10 which excludes somatic enquiry), favouring an inclusive approach to depression screening. Furthermore, the BDI (≥16) had fewer false positive and false negatives cases than the CDI (≥10). An inclusive approach has also been recommended by Drayer et al (2006) who found that depressed dialysis patients report more somatic symptoms than the non-depressed, and that physical symptoms relate more closely to depression than medical co-morbidity (Drayer et al., 2005). To note, the increased sensitivity and specificity of the BDI over the CDI may be the result of the diagnostic approach, which included somatic enquiry.

Two diagnostic approaches for depression in physical illnesses have been suggested previously; the research approach with adopts an exclusive criteria, and a clinical approach which employs an inclusive criteria (Cohen-Cole et al., 1993). The diagnostic criteria employed in this study (M.I.N.I) adopted an inclusive approach to assessment. This was done in-order to increase the sensitivity of our diagnostic assessment with which the BDI was compared. Following the administration of the M.I.N.I, 22.5% met the criteria for MDD. Estimated prevalence based upon a BDI≥16 ranged between 30 and 32.5%. These reports conform to the literature, as it is widely known that screen tools inflate estimates of depression among the medically ill. It is important to consider therefore, that estimates based upon symptom reports are at best indicators of potential depression. However they do meet their purpose in being able to assess the severity of depressive symptomatology, and remain a useful research tool. Indeed the data presented here, along with previous works (see chapter 4) suggest the utility of the BDI as a screening tool in HD patients.

This investigation was not without limitations. As noted previously the “CDI” has not been derived via factor analysis, thus its validity is questionable. In comparison the BDI has been subject to extensive psychometric evaluation, although not specifically in a renal population. This issue is addressed in the following chapter. Further, it is acknowledged that the consideration of other psychiatric co-morbidities, by means of a research interview, would have strengthened the data presented here. Lastly, due to the limited
sample size of our study we cannot exclude the possibility that the observed effects are due to confounding factors that cannot be fully evaluated due to limited power (i.e. differences between the depressed and non-depressed).

In response to increasing evidence highlighting the negative impact of depression upon the dialysis population, regular depression screening may be justified. Screening patients while actively dialysing may facilitate regular evaluation, increase identification of the condition, and allow monitoring of the effects of treatment interventions. For these reasons, bolstered by its appealing practicality, on-dialysis assessment was employed throughout the work presented in this thesis.
5.5 Results Part II: The assessment of illness perceptions on-dialysis

5.5.1 On- vs. off-dialysis illness perception assessment. Comparing dimension means

Table 5.6 shows the means for each of the illness perception dimensions, as assessed on and off-dialysis. In addition the internal reliability of each sub-scale on and off-dialysis is presented (α). Examining the dimension means reveals that patients reported greater perceptions of treatment control when assessed off-dialysis as compared to on-dialysis. Furthermore, emotion representations were greater when assessed on-dialysis, compared to off-dialysis reports. With the exception of treatment-control perceptions, all IPQ-R subscale dimensions had good internal reliability both on- and off-dialysis. Treatment control perceptions could only demonstrate modest internal reliability. LoA plots for each of the IPQ-R dimensions are displayed in figure 5.3 with the accompanying statistics displayed in table 5.7. While all plots display suitable agreement, emotional representations show a bias for on-dialysis assessment with a mean difference of 1.12 (95% CI 0.07 and 2.19). Treatment control perceptions were lower when assessed off-dialysis, biased towards off-dialysis assessment (mean difference= -1.05, 95% CI -0.14 and -1.95).

5.5.2 The timing of the off-dialysis IPQ-R assessment

In order to determine if the timing of the off-dialysis assessment influenced self-reported illness perceptions, comparisons were sought between those who were assessed pre- and post-dialysis. Mean scores on the IPQ-R dimensions did not differ significantly between patients assessed pre- and post dialysis.
Table 5.6: Comparison of the IPQ-R dimensions on- and off-dialysis.

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Mean on-dialysis</th>
<th>SD</th>
<th>Mean off-dialysis</th>
<th>SD</th>
<th>Significance (paired t-test)</th>
<th>On-Dialysis Cronbach’s Alpha</th>
<th>Off-dialysis Cronbach’s Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identity</td>
<td>5.42</td>
<td>3.55</td>
<td>5.75</td>
<td>3.52</td>
<td>t(39)=0.80</td>
<td>0.823</td>
<td>0.813</td>
</tr>
<tr>
<td>Timeline</td>
<td>25.61</td>
<td>4.50</td>
<td>25.76</td>
<td>4.50</td>
<td>t(39)=0.13</td>
<td>0.843</td>
<td>0.831</td>
</tr>
<tr>
<td>Cyclical</td>
<td>9.87</td>
<td>3.23</td>
<td>10.07</td>
<td>3.18</td>
<td>t(39)=0.97</td>
<td>0.758</td>
<td>0.843</td>
</tr>
<tr>
<td>Consequences</td>
<td>21.65</td>
<td>4.18</td>
<td>21.65</td>
<td>4.02</td>
<td>t(39)=0.05</td>
<td>0.61</td>
<td>0.661</td>
</tr>
<tr>
<td>Personal Control</td>
<td>18.07</td>
<td>4.39</td>
<td>18.37</td>
<td>5.20</td>
<td>t(39)=0.24</td>
<td>0.732</td>
<td>0.789</td>
</tr>
<tr>
<td>Treatment Control</td>
<td>14.63</td>
<td>3.04</td>
<td>15.68</td>
<td>2.75</td>
<td>t(39)=2.5*</td>
<td>0.405</td>
<td>0.438</td>
</tr>
<tr>
<td>Illness Coherence</td>
<td>19.81</td>
<td>4.64</td>
<td>19.73</td>
<td>4.46</td>
<td>t(39)=0.44</td>
<td>0.929</td>
<td>0.889</td>
</tr>
<tr>
<td>Emotion</td>
<td>17.12</td>
<td>5.43</td>
<td>16.0</td>
<td>5.26</td>
<td>t(39)=2.4*</td>
<td>0.866</td>
<td>0.854</td>
</tr>
</tbody>
</table>

* p<0.05 SD=Standard Deviation

Table 5.7: Level of agreement analysis for each of the IPQ-R dimensions, based upon the method described by Bland-Altman (1986).

<table>
<thead>
<tr>
<th>Dimension</th>
<th>BIAS (SE)</th>
<th>CI BIAS</th>
<th>Mean +2SD (UL)</th>
<th>CI (UL)</th>
<th>Mean -2SD (LL)</th>
<th>CI (LL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identity</td>
<td>-0.325 (0.4)</td>
<td>-1.14 0.49</td>
<td>4.8</td>
<td>3.38 6.21</td>
<td>-5.45 -6.86 -4.03</td>
<td></td>
</tr>
<tr>
<td>Timeline</td>
<td>-0.150 (0.5)</td>
<td>-1.24 0.94</td>
<td>6.71</td>
<td>4.81 8.61</td>
<td>-7.01 -8.91 -5.11</td>
<td></td>
</tr>
<tr>
<td>Cyclical</td>
<td>-0.205 (0.5)</td>
<td>-1.24 0.88</td>
<td>6.56</td>
<td>4.69 8.43</td>
<td>-6.96 -8.83 -5.09</td>
<td></td>
</tr>
<tr>
<td>Consequences</td>
<td>0.005 (0.5)</td>
<td>-1.0 1.0</td>
<td>6.41</td>
<td>4.63 8.18</td>
<td>-6.4 -8.17 -4.62</td>
<td></td>
</tr>
<tr>
<td>Personal Control</td>
<td>-0.300 (0.6)</td>
<td>-1.57 0.97</td>
<td>7.7</td>
<td>5.49 9.91</td>
<td>-8.3 -10.51 -6.09</td>
<td></td>
</tr>
<tr>
<td>Treatment Control</td>
<td>-1.050 (0.4)</td>
<td>-1.95 -0.14</td>
<td>4.63</td>
<td>3.06 6.2</td>
<td>-6.73 -8.3 -5.16</td>
<td></td>
</tr>
<tr>
<td>Illness Coherence</td>
<td>0.078 (0.5)</td>
<td>-0.89 1.0</td>
<td>6.14</td>
<td>4.46 7.81</td>
<td>-5.99 -7.66 -4.31</td>
<td></td>
</tr>
<tr>
<td>Emotion</td>
<td>1.120 (0.5)</td>
<td>0.07 2.19</td>
<td>7.73</td>
<td>5.9 9.55</td>
<td>-5.48 -7.3 -3.65</td>
<td></td>
</tr>
</tbody>
</table>

SE: Standard Error CI: Confidence Interval UL: Upper Limit LL: Lower Limit
Figure 5.3: LoA plots for each of the IPQ-R dimensions (mean bias, and mean ±2SD).
Figure 5.3: LoA plots for each of the IPQ-R dimensions (mean bias, and mean ±2SD) continued...
Figure 5.3: LoA plots for each of the IPQ-R dimensions (mean bias, and mean ±2SD) continued...
5.5.3 The interaction of depression and assessment condition upon illness perceptions

The interaction of depression (as assessed by the M.I.N.I) and assessment condition (on- vs. off-dialysis) upon illness perceptions was explored using mixed model ANOVAs. Unsurprisingly there was a main effect of depression upon emotional perceptions (table 5.8), that is depressed patients reported more emotional distress than the non-depressed patients. Furthermore emotion scores were greater when assessed on-dialysis as compared to off-dialysis. In addition there was a main effect of the assessment condition upon reported treatment control perceptions. Patients tended to report greater perceptions of treatment-control when not on dialysis. There were no significant interactions between assessment condition and depression.

Table 5.8. Mixed ANOVA for depression and assessment condition effects on IPQ-R scores.

<table>
<thead>
<tr>
<th>IPQ-R Dimension</th>
<th>Main effect of Assessment condition</th>
<th>Main effect of depression</th>
<th>Assessment X Depression Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identity</td>
<td>F(1,38) =0.347</td>
<td>F(1,38) =3.01</td>
<td>F(1,38) =0.18</td>
</tr>
<tr>
<td>Timeline</td>
<td>F(1,38) =0.515</td>
<td>F(1,38) =0.495</td>
<td>F(1,38) =3.01</td>
</tr>
<tr>
<td>Cyclical</td>
<td>F(1,38) =0.214</td>
<td>F(1,38) =0.013</td>
<td>F(1,38) =0.075</td>
</tr>
<tr>
<td>Consequences</td>
<td>F(1,38) =0.634</td>
<td>F(1,38) =2.72</td>
<td>F(1,38) =2.05</td>
</tr>
<tr>
<td>Personal Control</td>
<td>F(1,38) =1.35</td>
<td>F(1,38) =0.02</td>
<td>F(1,38) =2.0</td>
</tr>
<tr>
<td>Treatment Control</td>
<td>F(1,38) =5.87*</td>
<td>F(1,38) =0.917</td>
<td>F(1,38) =0.756</td>
</tr>
<tr>
<td>Illness Coherence</td>
<td>F(1,38) =0.277</td>
<td>F(1,38) =0.634</td>
<td>F(1,38) =1.29</td>
</tr>
<tr>
<td>Emotion</td>
<td>F(1,38) =4.49*</td>
<td>F(1,38) =13.6**</td>
<td>F(1,38) =0.409</td>
</tr>
</tbody>
</table>

*p<0.05 **p<0.01 F Statistics shown

5.5.4 The effect of depression upon symptom reports

The IPQ-R illness identity dimension concerns the reporting of physical symptoms that are attributed to ESRD. In addition, the number of endorsed physical symptoms regardless of their perceived aetiology was explored. The average number of reported symptoms was 7.4 (±3.6) when assessed on-dialysis, which did not differ significantly from symptoms reports made off-dialysis (7.6 ±3.4, t(39)=0.46, p=0.651). The mean number of symptoms reported in the off-dialysis condition assessed before treatment was 8.3 (±3.0), compared to 6.6 (±4.1) when assessed after dialysis. This difference was not significant (t(25.19)=1.4, p=0.168), although the effect size was moderate (d=0.58).
A mixed ANOVA model was performed to examine the following effects on reported somatic symptoms, 1) main effect of depression 2) main effect of assessment condition (on- vs. off-dialysis) and, 3) interactional effect (depression X assessment). There was a significant between-subject effect of depression upon reported symptoms scores (F(1,38)=7.6, p=0.009), with depressed patients scoring higher on the symptom scale than the non-depressed patients (table 5.9). There was no effect of the assessment condition upon reported symptoms (F(1,38)=0.32, p=0.57), however an interaction (depression X assessment condition) tending towards significance was observed (F(1,38)=3.04, p=0.08). The depressed patients reported more physical symptoms when on-dialysis and comparative less when off-dialysis (table 5.9).

**Table 5.9: Mean symptom scores across assessment conditions and depression groups.**

<table>
<thead>
<tr>
<th>Symptom score</th>
<th>Depressed</th>
<th>Non-Depressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-dialysis</td>
<td>10.4 (1.1)</td>
<td>6.5 (0.59)</td>
</tr>
<tr>
<td>Off-dialysis</td>
<td>9.6 (1.1)</td>
<td>7.0 (0.58)</td>
</tr>
</tbody>
</table>

*Data shown are Mean and Standard Error*

**5.6 Conclusion II (Illness Perceptions on- vs. Off-dialysis)**

The second part of this investigation was to ascertain the level of agreement between illness representations reported on-dialysis with off-dialysis reports. The results confirm the preceding finding in that on-dialysis IPQ-R assessment is viable. The trend for increased emotional representations while on-dialysis is similar to the findings for depression. Treatment control perceptions were also significantly different between the assessment conditions, with a bias for higher scores while off-dialysis. A point of caution is worthy here, as the treatment control subscale had low internal reliability (α). The potential issue here relates to the multiple facets of treatment associated with ESRD. Presumably, when patients are assessed on-dialysis “treatment” is being interpreted as “dialysis” because it is most salient to them at this time. One possible explanation for lower treatment control scores while on-dialysis may be that it is a relatively passive procedure, with most relying on the nursing team to set-up and administer the dialysis treatment. However differences
in personal control may have also been expected if this was solely the reason. At this point given the pilot nature of this work it is important not to accentuate this observation.

Although the aim was to evaluate the procedure of on-dialysis IPQ-R assessment, this work did provide an opportunity to comment on the psychology of symptom reporting. Given the afforded opportunity, I was guided by the work of Pennebaker (1982). According to Pennebaker self-focus to internal somatic activity is greater when the external environment lacks interest. It was assumed that dialysis is a tedious exercise, thus individuals may show a bias when reporting physical symptoms under such conditions. Although this study did not set out to explicitly test this hypothesis, there was no suggestive evidence for this theory. To note, the study here was an observational cohort, whereas previous studies have tended to be experimental investigations with student populations. Furthermore the underlying assumption that being on-dialysis increases self-focus was not tested directly. These factors combined with a relatively small sample size may have contributed to the null findings reported here.

Although no evidence was found for increased somatic symptom reporting while on-dialysis, it was found that depressed patients reported more somatic symptoms (as assessed by reported symptoms of the illness identity scale- regardless of believed cause) than non-depressed patients. These findings support past studies showing that individuals with high negative affectivity have a bias towards somatic activity (Stegen et al., 2001). More recent evidence has shown that depression is associated with inflated symptoms reports, more so than negative affectivity and neuroticism (Howren, Suls, & Martin, 2009).

Of further interest is the marginal interaction was between depression and assessment condition (on- vs. off-dialysis) upon reported somatic symptoms. The depressed patients appear to report more symptoms while on-dialysis as compared to off-dialysis, with the non-depressed showing no discernable difference. It is possible that for the depressed patients, the context of dialysis increased self-focused attention and thus their symptoms reports. These results lend some support for the “joint impact hypothesis” (Gendolla et al., 2005), which posits that both negative affect and self-focus enhance the reporting of physical symptoms. The data presented here suggest that the joint impact of self-focus (i.e. on-dialysis) and depression exacerbated symptom reports but was not necessary as
depression alone increased reporting of somatic symptoms. The evidence presented here supports the notion that depressed patients are more likely to report physical symptoms. The experience of physical symptoms could be inflated by the cognitive products of depression, for example overgeneralisation and magnification (Beck, 1967), or due to increased self-focus (Duval & Wicklund, 1972; Pyszczynski & Greenberg, 1987). Alternatively the reporting of increased physical symptoms may be due to greater underlying morbidity, which may increase depressive vulnerability.

Finally, there was a marginal interaction between depression and assessment condition with regards to time-line perceptions. It is possible that the increased somatic reporting of the depressed patients while on-dialysis has a subtle effect upon time-line cognitions. However again, due to the small sample size it is important not to accentuate this observation.

To conclude, while this section provides some interesting evidence regarding theories on the psychology of physical symptoms, the primary aim was to evaluate the procedure of on-dialysis IPQ-R assessment. By and large these data suggest that on-dialysis assessment would yield comparable data to assessments made off dialysis. Accordingly, on-dialysis IPQ-R and BDI assessments were employed in later studies presented in this thesis.Importantly, this method allowed HD patients to be assessed in a standardised manner.

5.7 General Remarks

This chapter presented a pilot study investigating the viability of on-dialysis BDI and IPQ-R assessments. Both questionnaires yield good agreement with their respective off-dialysis assessments. While the main focus here was on the procedure, the following chapter extends the inspection of the methods by evaluating the factor structure of the BDI among a large cross-sectional sample of haemodialysis patients.
Chapter 6

A Confirmatory Factor Analysis of the BDI-II in ESRD patients

6.1 Introduction

As discussed at some length in the preceding chapters, the assessment of depression is challenging when applied to the context of physical illness due to potentially overlapping somatic symptoms. The data presented in chapter five demonstrated that the BDI-II compares well with diagnostic standards for MDD providing the cut-off score is adjusted accordingly (≥16). The present chapter extends this work by examining the factor structure of the BDI-II, that is, do particular groups of questions measure particular underlying constructs of depression? The rationale was to establish whether the BDI-II measured distinct somatic and cognitive components of depression in ESRD patients.

The BDI in various forms has been used to assess depressive symptomatology in ESRD patients. Several authors have considered a 15 item non-somatic BDI-I total named the CDI, for use in ESRD patients (Kimmel, Weihs, & Peterson, 1993; Sacks et al., 1990). It was claimed that the CDI provided a better assessment of depression symptoms due to the removal of somatic items which would be confounded with the somatic symptoms of ESRD (Kimmel et al., 1993). Indeed this method was tentatively applied albeit it to the BDI-II in chapter 5 as measure of “cognitive depression”. However the conception of the CDI was not via factor analysis, thus the measurement structure of the BDI, or indeed BDI-II is not defined within this patient group. Beck adopted a similar notion with regards to the measurement of depression among physical illnesses, suggesting that somatic items may inflate estimates of depression. Accordingly Beck and co-workers developed the BDI-fast screen which is essentially the BDI-II minus somatic performance related questions (Beck, Steer, & Brown, 2000). However the authors stress that the BDI fast screen is not a substitute for BDI-II in medical inpatients (Beck et al., 2000). Furthermore, there is still contention regarding whether somatic items should be excluded from depression assessments among physical illnesses (Aikens et al., 1999). Considering the BDI-II’s underlying structure in dialysis patients using Confirmatory Factor Analysis (CFA see general methods), will enable a “cleaner” measurement of depression to be established and tested.
in subsequent chapters of this thesis. CFA achieves this cleaner measurement model because the technique enables estimates of variance relating to error (measurement error) to be removed, and can separate the variance between defined latent variables such as cognitive and somatic factors.

6.1.1 Studies of the factor structure of the BDI-II

The BDI-II was developed in accordance with symptoms from the DSM-IV (Beck, Steer, & Brown, 1996), and was intended as a global measure of the depression construct, although its specific structure has been of empirical interest (Beck, Steer, & Brown, 1996). However, due to the somatic items included in the BDI-II concerns have be raised with respect to its performance in the context of physical illness (Leentjens, Verhey, Luijckx, & Troost, 2000). Understanding the underlying structure of the BDI-II is important because sub-dimensions may be associated with different correlates (Mackinger & Svaldi, 2004). Furthermore particular factors may be more relevant and sensitive for detecting change in longitudinal analysis (Vanheule, Desmet, Groenvynck, Rosseel, & Fontaine, 2008), and it may be desirable to be able to differentiate predictive factors related to aspects of the depression construct (for example somatic vs. cognitive latent variables).

The structure of the BDI-II has received considerable empirical interest, although the results from numerous factor analyses have not been entirely consistent. Most studies report a two factor solution, representing cognitive and somatic latent variables that are well correlated. A two factor solution was evident in the initial study conducted by Beck et al (1996). Exploratory Factor Analysis (EFA) of the BDI-II administered to psychiatric patients (n=500) revealed oblique somatic-affective (SA) and cognitive (C) dimensions (Beck, Steer, & Brown, 1996). The SA and C factors consisted of 12 and 9 items respectively. The SA-C measurement model has received support from studies in general (Kojima et al., 2002), medical outpatient (Grothe et al., 2005) and psychiatric samples (Steer et al., 1999). Beck et al (1996) however failed to replicate the SA-C model in a student sample, but instead reported an alternative model consisting of a 16 item cognitive-affective (CA) dimension and a 5 item somatic (S) dimension. Several studies have also observed the CA-S structure in student samples (Steer & Clark, 1997; Wiebe & Penley, 2005). Two additional studies have confirmed the CA-S model, only however when some residual variances (error terms)
were allowed to correlate in the CFA model\(^6\) (Storch, Roberti, & Roth, 2004; Whisman, Perez, & Ramel, 2000).

Alternative models have been developed since several studies have failed to replicate the factor models proposed by Beck et al. Several alternative two factor models have been proposed (Arnau, Meagher, Norris, & Bramson, 2001; Dozois, Dobson, & Ahnberg, 1998; Steer et al., 1999; Viljoen, Iverson, Griffiths, & Woodward, 2003) while others report a three factor solutions with the inclusion of an “affective” factor (Beck, Steer, Brown, & van der Does, 2002; Buckley, Parker, & Heggie, 2001; Osman et al., 1997).

Arnau et al (2001) examined the BDI-II in a sample of medical patients and proposed a two factor solution comprising of a 12 item somatic-affective factor and an 8 item cognitive factor. Penley et al (2003) examined the factor model proposed by Arnau et al (2001) in 122 ESRD patients. This is the only published studied that has examined the factor structure of the BDI-II in this patient group. The results suggested that the data had a relatively poor fit to the Arnau et al factor model (CFI=0.75, RMSEA=0.1), although the authors claimed that the model was “adequate” (Penley et al., 2003). The failure to undertake model modification and consider alternative factor models as evident within the literature, are considerable limitations. Given this, the factor structure of the BDI-II has yet to be defined in ESRD.

More recently a three factor model consisting of a general depression factor (G) that loads onto all 21 BDI-II items, and two smaller orthogonal cognitive (C, 8 items) and somatic factors (S, 5 items) has been proposed (Ward, 2006). The Ward (2006) model also includes two minor two items factors called Anhedonia (An) and Self Criticism (SC) that were present in the Beck et al (1996) clinical sample analysis. The G-S-C model of Ward was tested in a sample of myocardial infarction patients (Thombs, Ziegelstein, Beck, & Pilote, 2008). In their analysis the G-S-C model provided better fit to the data than CA-S and SA-C two factor models, although the fit as examined by the CFI and RMSEA was marginal (0.92 and 0.07

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\(^6\) The authors allowed 3 pairs of meaningful item measurement errors to correlate suggesting that these residuals co-varied and that the items themselves were highly correlated.

\(^7\) As noted later in the methods both fit indexes indicated in the Penley et al study suggest poor fit based upon recommended guidelines, thus the model appears not to represent a robust factor structure in ESRD patients.
respectively). Simplifying the G-S-C by removing the Anhedonia and Self Criticism factors did not decrease the model fit (Thombs et al., 2008). This modified G-S-C model was recommended by Thombs et al (2008) as a novel approach to understanding the factor structure of the BDI-II in MI patients.

A comparative study of several BDI-II factor structures suggested that three-factor models including the G-S-C, provide better fit in both clinical and non-clinical samples as compared with two factor models (Vanheule et al., 2008). However none of the overall fit indices were particularly satisfactory. In an attempt to improve some of the models fit indexes, Vanheule et al (2008) used an item deletion algorithm to test whether removing some items led to more robust measurement models. Vanheule et al demonstrated that the model fit of the SA-C model (Beck et al., 1996) improved after the removal of 5 items (CFI=0.961 RMSEA=0.045). Similarly the three factor model of Buckley et al (2001) was improved after the deletion of 6 items (clinical patients CFI=0.960 RMSEA=0.047).

Given the various models proposed within the literature, the sole aim of the investigation presented here was to compare the relative fit of several two and three factor BDI-II models reviewed above, with data from dialysis patients using CFA. The objective was to identify the best fitting factorial structure for the BDI-II in ESRD patients.
6.2 Methods

6.2.1 Patients

BDI-II data from dialysis patients recruited from two multi-centered studies (one cross-sectional [n=215] and one longitudinal [n=160]) which are presented in the following empirical chapters (7 & 8 respectively), were pooled in order to maximise the sample size for CFA (total n=375). Data from the longitudinal study consisted of the baseline BDI-II assessment, as at this time point a greater number of patients were in the study. Details of the respective inclusion criteria, procedures, and study designs are described in the chapters that follow, in addition to the clinical and demographic characteristics pertaining to the two study samples (chapters 7&8).

6.2.2 Data Analysis

CFAs were evaluated in MPlus version 5.21 (Muthén & Muthén, 2007) using Weighted Least-Squares with Mean and Variance Adjustment (WLSMV) estimation. WLSMV was employed as the responses on the BDI-II items were skewed. Furthermore it is more appropriate to treat the ordinal BDI-II item scales as categorical variables. The WLSMV estimation unlike Maximum Likelihood (ML) procedures makes no assumptions about the distribution of the data (Muthén & Muthén, 2007) and models polychoric correlations. WLSMV estimation has been shown to produce accurate model statistics across models that vary in sample size, complexity and normality (Flora & Curran, 2004).

Missing data was minimal in the dataset. Overall 46 values were missing (0.6% of the total information). In order to retain all of the data for the CFAs, missing values were imputed with the item median. The median was used because imputing the mean was not possible as non-integer values cannot be analysed when using WLSMV estimation. Although not reported here, all the results shown in this chapter were replicated in a data-set that had the list-wise removal of missing data (n=356).

Eleven models were evaluated via CFA, 7 of which were two factor models and 4 of which were three factor models. A summary of the factors and items of these models are

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8 Total number of observations = 375 (patients) * 21 (items) =7875. Total missing cases, n =46. Percentage of missing data = 46/7875 *(100) =0.6.
presented in table 6.1. The structures of these various models were evaluated using chi-square goodness of fit test, which deriving the deviation between the reproduced covariance matrix with the observed covariance matrix. A non-significant chi-square is desired suggesting that the reproduced and observed covariance matrixes do not differ significantly hence the data fits the proposed model structure. However as described in the general methods the chi-square statistic is sensitive to sample size (Ullman, 2006) thus several fit indices were also evaluated. The comparative fit index (CFI) is an incremental fit index that compares the proposed model with the null model, and uses an approach based on the noncentral chi-square distribution (Bentler, 1990). A CFI ≥0.95 indicates good fit (Hu & Bentler, 1999). The Tucker Lewis Index (TLI) was also employed, which has the similar interpretation to the CFI but also considers the number of parameters (Tucker & Lewis, 1973). A final index, The Root Mean Square Error of Approximation (RMSEA) considers model complexity. A RMSEA <0.05 is considered to demonstrate reasonable fit, while a value of >0.1 suggests poor fit (Browne & Cudeck, 1993).

The best fitting models based upon these criteria were subject to model modification, in order to see whether the fit could be further improved (see general methods).
Table 6.1: Summary of the factors and items proposed by previous authors for the BDI-II.

| Item | Model | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
|      | Factor | Sadness | Pessimism | Past Failure | Loss of Pleasure | Guilt | Punishment | Self-Dislike | Self-Criticism | Suicide | Crying | Agitation | Loss of interest | Indifference | Worthlessness | Loss ofEnergy | Changes in sleep | Irritability | Change in appetite | Concentration | Fatigue | Loss of interest in sex |
|      | C    | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C    | Dozois et al (1998) | CA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| E    | Arnau et al (2001) | SA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| I    | Vanheule et al (2008) -Beck | C   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| J    | Vanheule et al (2008) -Buckley | C   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

6.3 Results

The average age of the pooled sample was 59.1 (±15.7) years. Of the 375 patients, 66.9% were male and the majority were white (89.3%). The median dialysis vintage was 323 (IQR 1397) days. The majority of patients were receiving HD treatment (92.5%) with the reminding on PD. A BDI≥16 was evident in 28% of the sample indicating significant depressive symptomatology. Descriptive characteristics of the BDI-II items are displayed in table 6.2. The mean BDI-II score for the pooled sample was 12.1 (±8.4). The mean BDI-II score from the baseline collection of the longitudinal study was 12.1 (8.7), which did not differ significantly from the mean observed in the cross-sectional sample (12.2 ±8.2, t(373)=0.15, p=0.988). The distributions of the BDI-II scores for each of the study samples are shown in figure 6.1. Examination figure 6.1 shows that the data had a similar distribution across the two sample data sets in that both display a slight positive skew.

![Figure 6.1: Distributions of the BDI-II total scores across the two study data sets.](image)

Model fit statistics for each of the two, and three factor BD-II models tested are presented in table 6.3. The two factor models (models A-F) had moderate levels of fit, accompanied by the two of the three factor models (models G & H). The shortened SA-C model of Beck et al (1996) and the shortened 3 factor model of Buckley et al (2001), as devised by Vahnheule
et al (2008, models I&J respectively, table 6.3), showed improved fit as compared to models A-H, evident by CFI’s in the order of 0.95 and RMSEA’s near 0.05.

**Table 6.2:** Item characteristics of the BDI-II: measures of central tendency, variation, and distribution.

<table>
<thead>
<tr>
<th>Item</th>
<th>Mean</th>
<th>S.E</th>
<th>S.D</th>
<th>Median</th>
<th>IQR</th>
<th>Skewness</th>
<th>Kurtosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI1</td>
<td>0.30</td>
<td>0.03</td>
<td>0.54</td>
<td>0</td>
<td>1</td>
<td>2.05</td>
<td>5.25</td>
</tr>
<tr>
<td>BDI2</td>
<td>0.62</td>
<td>0.04</td>
<td>0.76</td>
<td>0</td>
<td>1</td>
<td>1.27</td>
<td>1.52</td>
</tr>
<tr>
<td>BDI3</td>
<td>0.34</td>
<td>0.04</td>
<td>0.71</td>
<td>0</td>
<td>1</td>
<td>2.01</td>
<td>3.11</td>
</tr>
<tr>
<td>BDI4</td>
<td>0.68</td>
<td>0.04</td>
<td>0.75</td>
<td>0</td>
<td>1</td>
<td>1.15</td>
<td>1.49</td>
</tr>
<tr>
<td>BDI5</td>
<td>0.29</td>
<td>0.03</td>
<td>0.57</td>
<td>0</td>
<td>0</td>
<td>1.96</td>
<td>3.55</td>
</tr>
<tr>
<td>BDI6</td>
<td>0.26</td>
<td>0.04</td>
<td>0.75</td>
<td>0</td>
<td>0</td>
<td>2.95</td>
<td>7.60</td>
</tr>
<tr>
<td>BDI7</td>
<td>0.41</td>
<td>0.03</td>
<td>0.66</td>
<td>0</td>
<td>1</td>
<td>1.59</td>
<td>2.24</td>
</tr>
<tr>
<td>BDI8</td>
<td>0.37</td>
<td>0.03</td>
<td>0.64</td>
<td>0</td>
<td>1</td>
<td>1.99</td>
<td>4.40</td>
</tr>
<tr>
<td>BDI9</td>
<td>0.14</td>
<td>0.02</td>
<td>0.39</td>
<td>0</td>
<td>0</td>
<td>3.10</td>
<td>11.52</td>
</tr>
<tr>
<td>BDI10</td>
<td>0.37</td>
<td>0.04</td>
<td>0.72</td>
<td>0</td>
<td>1</td>
<td>2.23</td>
<td>4.76</td>
</tr>
<tr>
<td>BDI11</td>
<td>0.45</td>
<td>0.03</td>
<td>0.62</td>
<td>0</td>
<td>1</td>
<td>1.36</td>
<td>2.20</td>
</tr>
<tr>
<td>BDI12</td>
<td>0.42</td>
<td>0.04</td>
<td>0.75</td>
<td>0</td>
<td>1</td>
<td>2.03</td>
<td>3.87</td>
</tr>
<tr>
<td>BDI13</td>
<td>0.34</td>
<td>0.03</td>
<td>0.63</td>
<td>0</td>
<td>1</td>
<td>2.05</td>
<td>4.60</td>
</tr>
<tr>
<td>BDI14</td>
<td>0.37</td>
<td>0.03</td>
<td>0.63</td>
<td>0</td>
<td>1</td>
<td>1.51</td>
<td>1.32</td>
</tr>
<tr>
<td>BDI15</td>
<td>1.22</td>
<td>0.03</td>
<td>0.64</td>
<td>0</td>
<td>1</td>
<td>0.35</td>
<td>0.36</td>
</tr>
<tr>
<td>BDI16</td>
<td>1.23</td>
<td>0.05</td>
<td>0.89</td>
<td>0</td>
<td>1</td>
<td>0.48</td>
<td>-0.41</td>
</tr>
<tr>
<td>BDI17</td>
<td>0.44</td>
<td>0.03</td>
<td>0.62</td>
<td>0</td>
<td>1</td>
<td>1.28</td>
<td>1.43</td>
</tr>
<tr>
<td>BDI18</td>
<td>0.82</td>
<td>0.04</td>
<td>0.79</td>
<td>1</td>
<td>1</td>
<td>0.72</td>
<td>0.02</td>
</tr>
<tr>
<td>BDI19</td>
<td>0.57</td>
<td>0.04</td>
<td>0.68</td>
<td>0</td>
<td>1</td>
<td>0.89</td>
<td>-0.00</td>
</tr>
<tr>
<td>BDI20</td>
<td>1.11</td>
<td>0.04</td>
<td>0.75</td>
<td>1</td>
<td>0</td>
<td>0.60</td>
<td>0.44</td>
</tr>
<tr>
<td>BDI21</td>
<td>1.33</td>
<td>0.06</td>
<td>1.16</td>
<td>1</td>
<td>3</td>
<td>0.29</td>
<td>-1.38</td>
</tr>
</tbody>
</table>

**BDITOTAL**: 12.1 0.43 8.40 11 10 1.08 1.229

S.E = Standard Error  S.D = Standard Deviation  IQR= Inter-quartile range
### Table 6.3: Summary of CFA results for various BDI-II models.

<table>
<thead>
<tr>
<th>Model</th>
<th>Chi-Square</th>
<th>df</th>
<th>P value</th>
<th>CFI</th>
<th>TLI</th>
<th>RMSEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>266.2</td>
<td>76</td>
<td>&lt;0.001</td>
<td>0.913</td>
<td>0.964</td>
<td>0.082</td>
</tr>
<tr>
<td>B</td>
<td>261.3</td>
<td>77</td>
<td>&lt;0.001</td>
<td>0.916</td>
<td>0.965</td>
<td>0.080</td>
</tr>
<tr>
<td>C</td>
<td>271.0</td>
<td>76</td>
<td>&lt;0.001</td>
<td>0.911</td>
<td>0.963</td>
<td>0.083</td>
</tr>
<tr>
<td>D</td>
<td>288.9</td>
<td>76</td>
<td>&lt;0.001</td>
<td>0.903</td>
<td>0.959</td>
<td>0.086</td>
</tr>
<tr>
<td>E</td>
<td>284.7</td>
<td>76</td>
<td>&lt;0.001</td>
<td>0.905</td>
<td>0.960</td>
<td>0.086</td>
</tr>
<tr>
<td>F</td>
<td>284.7</td>
<td>76</td>
<td>&lt;0.001</td>
<td>0.905</td>
<td>0.960</td>
<td>0.086</td>
</tr>
<tr>
<td>G</td>
<td>271.6</td>
<td>76</td>
<td>&lt;0.001</td>
<td>0.910</td>
<td>0.962</td>
<td>0.084</td>
</tr>
<tr>
<td>H</td>
<td>237.8</td>
<td>75</td>
<td>&lt;0.001</td>
<td>0.926</td>
<td>0.968</td>
<td>0.076</td>
</tr>
<tr>
<td>I</td>
<td>140.1</td>
<td>57</td>
<td>&lt;0.001</td>
<td>0.950</td>
<td>0.977</td>
<td>0.062</td>
</tr>
<tr>
<td>J</td>
<td>112.8</td>
<td>52</td>
<td>&lt;0.001</td>
<td>0.952</td>
<td>0.977</td>
<td>0.056</td>
</tr>
<tr>
<td>K</td>
<td>185.3</td>
<td>75</td>
<td>&lt;0.001</td>
<td>0.950</td>
<td>0.979</td>
<td>0.063</td>
</tr>
<tr>
<td>L</td>
<td>143.6</td>
<td>75</td>
<td>&lt;0.001</td>
<td>0.969</td>
<td>0.987</td>
<td>0.049</td>
</tr>
<tr>
<td>M</td>
<td>144.5</td>
<td>75</td>
<td>&lt;0.001</td>
<td>0.968</td>
<td>0.987</td>
<td>0.050</td>
</tr>
</tbody>
</table>

~Estimation: WLSMV. CFI = Comparative Fit Index. TLI= Tucker Lewis Index. RMSEA= Root Mean Square Error of Approximation.

The G-S-C model of Ward (2006, model K in table 6.3) demonstrated comparable good fit to the models of Vanheule et al. To note, in the G-S-C model the minor factor of Anhedonia and Self-Criticism have equality constraints\(^9\) placed on their factors loadings in order for the model to be identified. Given that models of Vanheule et al were already modified via a deletion algorithm, Ward’s G-S-C was selected for model modification in the present analysis. An examination of the modification indexes suggested that item 1 (sadness) would improve the model fit if loaded onto the cognitive latent variable (Modification index= 16.67). Furthermore loading item 21 (sex) onto the somatic latent variable suggested a modification index of 31.13. Since these changes appeared to be theoretically viable the G-S-C model was modified with these changes and reanalysed. The modified model (model L) showed improved fit over the standard G-S-C model (CFI= 0.969, RMSEA = 0.049). The standardised factor loadings, \(r^2\) and residual variances for this modified G-S-C model are displayed in table 6.4. All the factor loadings (model L) were significant except both of the

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\(^9\) Equality constraints were placed as only two items were specified to load onto a factor, thus the model could not be identified. Constraining the variances to be equal allows the model to be identified.
items on the SC factor, which were self-dislike and self-criticism. Factor loadings on the G factor were all reasonably high, with 14 of the 21 items having standardised loadings in excess of 0.60.

The G-S-C model was then simplified by excluding the minor factors self-criticism and anhedonia, which has been shown by others not to affect the overall model fit (Thombs et al., 2008). Indeed, in the present analysis, removing these two factors from the modified G-S-C model did not affect the model fit (model M, table 6.3 CFI=0.968 RMSEA=0.05). This final G-S-C model is depicted in figure 6.2. Each of the G-S-C factors had good internal reliability (G $\alpha=0.89$, S $\alpha=0.66$ and, C $\alpha=0.84$).

Correlations were sought between the G-S-C latent factors and the total BDI-II scores. The general depression factor (G) correlated highly with total BDI-II scores ($r=0.9$, $p<0.001$), explaining 81% of the variance. Correlations between the S and C factors with the total BDI-II scores were $r=0.254$ ($p<0.001$), and $r=0.18$ ($p<0.001$) respectively. Taken together, all three factors (G-S-C) explained 91% of the total variance in BDI-II total scores.
Table 6.4: Standardised factor solution from the CFA of the modified G-S-C model.

<table>
<thead>
<tr>
<th>Number</th>
<th>Item description</th>
<th>G</th>
<th>S</th>
<th>C</th>
<th>SC</th>
<th>An</th>
<th>R²</th>
<th>Residual Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI1</td>
<td>Sadness</td>
<td>0.707</td>
<td>0.317</td>
<td></td>
<td></td>
<td>0.600</td>
<td>0.400</td>
<td></td>
</tr>
<tr>
<td>BDI2</td>
<td>Pessimism</td>
<td>0.652</td>
<td>0.228</td>
<td></td>
<td></td>
<td>0.477</td>
<td>0.523</td>
<td></td>
</tr>
<tr>
<td>BDI3</td>
<td>Past Failure</td>
<td>0.628</td>
<td>0.589</td>
<td></td>
<td></td>
<td>0.742</td>
<td>0.258</td>
<td></td>
</tr>
<tr>
<td>BDI4</td>
<td>Pleasure</td>
<td>0.723</td>
<td>0.296</td>
<td></td>
<td></td>
<td>0.611</td>
<td>0.389</td>
<td></td>
</tr>
<tr>
<td>BDI5</td>
<td>Guilt</td>
<td>0.616</td>
<td>0.388</td>
<td></td>
<td></td>
<td>0.530</td>
<td>0.470</td>
<td></td>
</tr>
<tr>
<td>BDI6</td>
<td>Punishment</td>
<td>0.497</td>
<td>0.470</td>
<td></td>
<td></td>
<td>0.469</td>
<td>0.531</td>
<td></td>
</tr>
<tr>
<td>BDI7</td>
<td>Self-Dislike</td>
<td>0.780</td>
<td>0.326</td>
<td>0.143</td>
<td></td>
<td>0.735</td>
<td>0.265</td>
<td></td>
</tr>
<tr>
<td>BDI8</td>
<td>Self-Criticism</td>
<td>0.670</td>
<td>0.290</td>
<td>0.143</td>
<td></td>
<td>0.554</td>
<td>0.446</td>
<td></td>
</tr>
<tr>
<td>BDI9</td>
<td>Suicide</td>
<td>0.659</td>
<td>0.296</td>
<td></td>
<td></td>
<td>0.522</td>
<td>0.478</td>
<td></td>
</tr>
<tr>
<td>BDI10</td>
<td>Crying</td>
<td>0.691</td>
<td></td>
<td></td>
<td></td>
<td>0.477</td>
<td>0.523</td>
<td></td>
</tr>
<tr>
<td>BDI11</td>
<td>Agitation</td>
<td>0.751</td>
<td></td>
<td></td>
<td></td>
<td>0.564</td>
<td>0.478</td>
<td></td>
</tr>
<tr>
<td>BDI12</td>
<td>Interest</td>
<td>0.753</td>
<td></td>
<td>0.296</td>
<td></td>
<td>0.655</td>
<td>0.345</td>
<td></td>
</tr>
<tr>
<td>BDI13</td>
<td>Indecisiveness</td>
<td>0.763</td>
<td></td>
<td></td>
<td></td>
<td>0.583</td>
<td>0.417</td>
<td></td>
</tr>
<tr>
<td>BDI14</td>
<td>Worthlessness</td>
<td>0.741</td>
<td></td>
<td>0.374</td>
<td></td>
<td>0.690</td>
<td>0.310</td>
<td></td>
</tr>
<tr>
<td>BDI15</td>
<td>Loss of Energy</td>
<td>0.530</td>
<td>0.671</td>
<td></td>
<td></td>
<td>0.731</td>
<td>0.269</td>
<td></td>
</tr>
<tr>
<td>BDI16</td>
<td>Sleep</td>
<td>0.419</td>
<td>0.311</td>
<td></td>
<td></td>
<td>0.272</td>
<td>0.728</td>
<td></td>
</tr>
<tr>
<td>BDI17</td>
<td>Irritability</td>
<td>0.745</td>
<td></td>
<td></td>
<td></td>
<td>0.555</td>
<td>0.445</td>
<td></td>
</tr>
<tr>
<td>BDI18</td>
<td>Appetite</td>
<td>0.448</td>
<td>0.138~</td>
<td></td>
<td></td>
<td>0.219</td>
<td>0.781</td>
<td></td>
</tr>
<tr>
<td>BDI19</td>
<td>Concentration</td>
<td>0.685</td>
<td>0.127~</td>
<td></td>
<td></td>
<td>0.485</td>
<td>0.515</td>
<td></td>
</tr>
<tr>
<td>BDI20</td>
<td>Fatigue</td>
<td>0.497</td>
<td>0.619</td>
<td></td>
<td></td>
<td>0.631</td>
<td>0.369</td>
<td></td>
</tr>
<tr>
<td>BDI21</td>
<td>Sex</td>
<td>0.275</td>
<td>0.374</td>
<td></td>
<td></td>
<td>0.215</td>
<td>0.785</td>
<td></td>
</tr>
</tbody>
</table>


Unless otherwise indicated all p<0.01. ~p<0.05 ³p>0.05
Figure 6.2: Modified G-S-C model for the BDI-II
6.4 Discussion
This chapter is the second in succession to give specific attention to the measurement of depression symptoms in ESRD patients. The attention afforded in the present chapter was to examine the underlying structure of the BDI-II by means of confirmatory factor analysis. The importance of this undertaking extended beyond conceptual interest; rather it allowed a robust latent measurement model to be defined that could then be modelled in future large scale investigations, and allowed the validity of the measure to be evaluated in this patient group.

In order to achieve this aim several CFAs evaluated the relative fit of specified two, and three factor structures for the BDI-II in a sample of dialysis patients in the data collected for this thesis. The main findings support data from previous publications suggesting that an alternative three factor model containing a general depression factor and two orthogonal somatic and cognitive factors have better fit than two factor models (Thombs et al., 2008; Ward, 2006). Furthermore, modification of the G-S-C by loading sadness onto the cognitive factor and sex onto the somatic factor, improved the G-S-C model fit further. The nature of the factor loadings were similar to those reported by Thomb et al (2008) who confirmed the G-S-C structure in a sample of myocardial infarction patients. As with Thomb et al, the data here provided little support for the inclusion of the Anhedonia and Self-Criticism factors. Their removal did not impact upon the models overall fit.

The modified G-S-C presented here provides an alternative description of the measurement structure of the BDI-II, although the findings here may be specific to the ESRD population. As reviewed by others (Thombs et al., 2008; Ward, 2006) the G-S-C model has several conceptual and empirical advantages over common two factor approaches. The cognitive and somatic latent factors in two factor models are highly correlated thus multicollinearity remains an issue when regressing both factors in a chosen analysis. Furthermore, several items fail to fit onto either cognitive or somatic factors thus the distinction between these two latent factors is not robust (Thombs et al., 2008). Moreover, Steer et al (1999) reports that two factor models are not stable because dimensions tend to shift in different samples. The G-S-C model is advantageous as its structure appears relatively stable (Ward, 2006). The notion of a general depression factor conforms with the proposed rational of
the BDI-II as *global measure* of depression severity (Beck, Steer, & Brown, 1996). Moreover the G-S-C model allows the variance from the orthogonal cognitive and somatic latent variables to be *separated* from the general depression factor. The cognitive and somatic distinction in the G-S-C model allows a “cleaner” measure of the underlying latent constructs that are not confounded by an underlying depression factor, as may be the case in two factor models (i.e. SA-C and CA-S). Although the G factor contributes most to the explained variance, the cognitive and somatic constructs explain a small yet unique amount of additional variance. It is therefore possible to model and test specific questions that pertain to the cognitive and somatic latent variables after separating the common variance associated with general depressive symptoms. However a caveat here is that because the bi-factor G-S-C model separates the variance between the three factors, in order to regress the latent variables upon potential independent variables (predictors) would require a very large sample size.

The G factor correlated highly with the total BDI-II score. Taken together the three factors of the G-S-C explained over 90% of the variance in the total BDI-II scores. This suggests that using a total BDI-II score in various analyses in ESRD patients would produce similar findings to those of a measurement model containing a general depression factor. Given that SEM may not be appropriate in some instances, and for most studies issues of power may prevent the use of the bi-factor model, a total BDI-II score appears to be a good indicator of global depressive symptoms. For these reasons a total BDI score will be utilised in the empirical studies that follow.

Finally, these results shown here have significant implications for the “CDI”, which has been used in several ESRD studies to assess apparent “cognitive” depression (Sacks et al., 1990). Although the CDI was derived from the BDI-I, whereas the BDI-II was used here, it is clear that two factor models of depression (cognitive vs. somatic) do not represent the most robust model for depression in ESRD. Further, as suggested elsewhere removing somatic symptoms may also reduce the BDI-II’s content validity (Penley, Wiebe, & Nwosu, 2003). It is proposed that the modified G-S-C model presented here provides a better understanding and measurement model for the BDI-II as applied to ESRD patients.
The strengths of this analysis include the consideration and evaluation of several models in a reasonably large sample of dialysis patients. However the small number of PD patients in the analysis was a limitation. This prohibited comparison of the BDI-II’s structure between HD and PD patients using multi-group CFA analysis. While the G-S-C appears relatively robust, it would be of interest to examine any potential differences between treatment modalities in future investigations. Further the “construct” of depression in this setting was only considered in English speaking patients. Cultural representations and constructs of depression may differ from measurement models identified in English speaking patients. Developing reliable measures of depression among the multi-ethnic dialysis population is required if clinicians and researchers alike are to fully appreciate the extent of depression in ESRD and identify the associated antecedents. This however is likely to be a considerable undertaking.

6.5 General Remarks

The BDI-II provides a good measure of global depressive symptoms in ESRD patients supporting its validity in this setting. The modified G-S-C model is a novel approach to understanding the underlying latent constructs of depression in ESRD as measured by the BDI-II, which can be modelled in subsequent analyses. Given the potential issues surrounding depression assessment in chronic illnesses, the G-S-C model may provide a useful measurement approach in other diseases (see Thombs et al., 2008). This is potentially useful as comparisons between disease groups with regards to antecedents and time-course could be sought.

Up to this point considerable attention has been devoted to the assessment and measurement of depression in ESRD. Not only has this empirical work assessed the validity of the measure and identified a latent measurement model for the BDI-II in ESRD patients, it has also established a practical procedure in which the BDI-II can be administered.

The next chapter directs attention to the thesis argued in this body of work; providing evidence for the association between illness perceptions and depression in a multi-centred cross-sectional study of established HD patients.
Chapter 7

The Association between Depression and Illness Representations in Haemodialysis Patients: A Cross-sectional Study

7.1 Introduction

The aetiology of depression can be considered to involve biological, psychological and social vulnerabilities, which are by no means independent antecedents. These vulnerabilities are amplified in the context of chronic physical disease, and across a variety of physical illnesses depression is known to be more common than in general populations (Creed & Dickens, 2007). Given this, it is important to identify factors that distinguish the depressed from the non-depressed within the context of chronic physical disease.

The focus of the present chapter is to understand whether illness perceptions pertaining to the CSM are associated with depression in established haemodialysis patients. As described in chapter 3, illness representations are important contributors to psychological adjustment including depression. Furthermore, examining illness perceptions in relation to depression is of interest since both are associated with adverse outcomes among patients with physical illnesses, and indeed in ESRD. Illness representations set the targets for self-regulation in order to control and resolve health threats. Maladaptive perceptions could therefore influence the selection of maladaptive coping procedures and behaviours that increase an individual’s vulnerability for depression. For example, there is evidence that stress and coping are associated with depression and psychological distress in dialysis patients (Welch & Austin, 2001), which supports the wider literature (Goldstein, Holland, Soteriou, & Mellers, 2005; Lazarus & Folkman, 1984). Furthermore, illness perceptions have been shown to predict self-efficacy (Lau-Walker, 2004), and self-efficacy has been associated with depression among patients with physical illness (Tedman, Thornton, & Baker, 1995; Tsay & Chao, 2002). However, the importance of coping and concepts of control such as self-efficacy, as mediators between illness perceptions and outcomes have received limited empirical support (Edgar & Skinner, 2003; Evans & Norman, 2009; Heijmans, 1999; Moss-Morris, Petrie, & Weinman, 1996). Goldstein et al (2005) reported that coping mediated the association between illness identity and depression in patients with epilepsy, although the small sample size and cross-sectional design are limitations. In addition, behavioural...
disengagement and restraint coping mediated the relationship between illness perceptions (cure/control and consequences) and depression in a sample of patients suffering from irritable bowel syndrome (Rutter & Rutter, 2002), although in a follow-up investigation there was no evidence of mediation over time (Rutter & Rutter, 2007).

The contention surrounding coping as a mediator between illness representation and outcome may have its roots in the conceptualisation of the CSM, and how it views coping. The treatment of “coping” in the CSM deviates from factor analytic approaches such as the stress coping model (Lazarus & Folkman, 1984) which are arguably over simplistic categorisations. Indeed using such approaches, coupled with cross-sectional designs, make it hard to tease apart coping from illness perceptions. For example does the perception that a disease is acute reflect avoidant coping or a genuine belief about the disease’s expected time-line? As articulated recently, depression in physical illnesses may be the product of effective coping procedures undertaken to deal with disease management (Detweiler-Bedell et al., 2008). It is argued that the under-regulation of mood may result from illness representations that define the strategies and behaviours that are adaptive for disease management, yet to the disadvantage of emotion regulation (Baumeister & Heatherton, 1996; Detweiler-Bedell et al., 2008).

Negative cognitions are cardinal features of the cognitive theory of depression (Beck, 1967) thus according to principles of cognitive theory, it may be speculated that negative illness perceptions may increase the vulnerability for depression via the activation of depressive schema. Alternatively, the relationship between illness perceptions and depression may also reflect underlying morbidity. Indeed others have reported an interaction between illness severity and illness perceptions as a predictor of depression (Schiaffino et al., 1998). However this study was conducted in RA patients where symptomatic cyclical fare ups may lead to temporal changes in illness perceptions. A longitudinal study looking at changes in health related QoL in Coronary Heart Disease patients, found that illness perceptions mediated the association between disease severity and wellbeing (Aalto et al., 2006). This suggests a dynamic relationship between disease status and illness representations. In addition it is well established that illness perceptions predict functional status in several diseases including MI and RA patients (Bijsterbosch et al., 2009; Petrie et al., 2002; Petrie et al., 1996). The association between functional status (in terms of disability) and depression
is also known (Buchi et al., 1998; Egede, 2007; McFarlane & Brooks, 1988). However, the relationship between co-morbidity and depression is less understood. In dialysis patients some data reports a significant association between extra renal co-morbidity and depression (Brown et al., 2010; Hedayati et al., 2008; Lopes et al., 2002; Simic Ogrizovic et al., 2009), although other studies have found no relationship (Drayer et al., 2006; Kimmel, Peterson et al., 1998).

There is evidence that the relationship between depression and physical disease is bidirectional. Depression has been found to influence the progression of disease; and also depression can result from the onset of disease (Creed & Dickens, 2007; Steptoe, 2007). Prospective studies in RA suggest that medical intervention alone does little to predict or improve mood. Rather, it is the perceptions around the illness that are more influential upon subsequent mood and indeed health-related outcomes, rather than objective measures of disease or co-morbidity (Jopson & Moss-Morris, 2003; Petrie et al., 1996; Sacks et al., 1990; Sharpe, Sensky, & Allard, 2001). Despite good evidence that illness representations predict depression among other illness groups (Dickens et al., 2008; Jopson & Moss-Morris, 2003; Scharloo et al., 1999) no study has addressed the relationship in ESRD.

As reviewed in chapter 3, illness perceptions are associated with QoL in dialysis patients. Timmers et al (2008) reported that illness identity, consequences, personal control, and emotional representations, were associated with the physical component score of the SF-36, explaining an additional 30% of the variance above and beyond clinical and demographic variables. Griva et al (2009) reported that treatment and illness perceptions are associated with QoL. After controlling for demographic and dialysis related factors, both perceptions of treatment disruptiveness and illness consequences were associated with the mental functioning component of the SF-36. This data suggests that a major influence of QoL in ESRD relates to the interpretation and regulation of illness. Given the association between quality of life and illness perception reported in dialysis patients it was envisaged that depression and illness perceptions would share a close relationship.

Depression is a well established psychopathology in ESRD, yet illness-related psychological and clinical factors are not well understood in terms of their relationship with affect. The
CSM provides a theoretical platform to explain how patients understand and adapt as a part of continuous self-regulatory efforts, and may therefore aid in the explanation of depression among HD patients. The present study examined depression symptoms in a well establish multi-centred sample of haemodialysis patients using the BDI-II. In order to provide an estimate of depression a BDI≥16 was employed to define potential cases. The nature of illness perceptions in relation to affect was explored. In light of the findings from past studies investigating the association between illness perceptions and depression, the following hypotheses were constructed:

1) Clinical factors will be largely unrelated to depression.

2) Consequences and control perceptions would be associated with depression.

3) Illness perceptions will be strong predictors of depression, and provide a significant improvement in explained variance, above and beyond clinical and demographic factors.

7.2 Methods

7.2.1 Patients

Patients established on an in-hospital haemodialysis programme from three UK NHS renal centers (Lister n=155, Royal Free n=15, and Addenbrooke’s n=55) were recruited into the study (n=215). Patients were eligible for inclusion if the following criteria was met; i) no known significant visual or physical impairment that would prevent the completion of the questionnaires, ii) fluency in verbal and written English language, (iii) not hospitalised at the time of assessment, iv) had been receiving haemodialysis for >6 months and v) no cognitive impairment, as indicated by an age adjusted score of <22 on the Mini Mental State Examination (Folstein et al., 1975).

7.2.2 Materials

Demographic questionnaire: Information on age, gender, ethnicity, marital-status, and work-status were collected by means of a patient questionnaire. Transplant status was determined via self-report. Patients were asked if they were currently on the transplant waiting list (yes, no or don't know).
The Revised Illness Perception Questionnaire (IPQ-R): As described in chapter 4. The sample size permitted Principle Component Analysis on the 18 causal items of the IPQ-R as recommended by (Moss-Morris et al., 2002). Initially all the causal items were entered into the analysis. Item 2 (hereditary cause) was removed due an insufficient Measure of Sampling Adequacy (MSA <0.5) revealed in the anti-image matrix. Item 7 (pollution) was also removed as it loaded onto more than one factor. Analysis of the remaining 16 items with direct Oblimin rotation revealed a three factor solution (see table 7.1). All extracted factors had Eigen-values >1.1. The first factor consisted of 7 items and demonstrated good internal reliability (α=0.87). These items pertained to attributions surrounding stress, emotion, and behaviour, thus was labelled psychological causes. The second factor labelled risk factors contained 6 items which largely oriented around general risk factors for illness, including smoking and ageing. This second factor also demonstrated adequate reliability (α=0.80). A final factor labelled external causes consisted of 3 items and had relative low internal consistency (α=0.52).

Depression Symptoms: Depression symptoms were assessed via the Beck Depression Inventory (BDI-II) as described in Chapter 4. A BDI≥16 was employed to define patients with probable depression (see chapter 5). The BDI was treated as a categorical outcome (i.e. BDI≥16) because the aim here was to examine illness perceptions that were associated with a group of patients who are likely to being suffering from depression as suggested by an adjusted BDI cut-off score.

7.2.3 Clinical Data

Functional Status and Comorbidity: Karnofsky Performance Score was employed to assess functional status (see chapter 4). Comorbidity was assessed using a semi-quantitative technique (Chandna et al., 1999), scored by consultant nephrologist who assigned a severity score for each patient (1= no co-morbidity, 2= mild moderate co-morbidity, 3= severe co-morbidity. This method has been described previously in the general methods (see chapter 4).

Clinical parameters: Standard haematological and biochemical parameters are collected as a part of the routine care of patients within the service. These included Haemoglobin, Albumin, CRP and dialysis Kt/V (see methods).
Table 7.1: Principle Component analysis of the IPQ-R causal items: Structure Matrix of factors and their loadings.

<table>
<thead>
<tr>
<th>Factor</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor 1. Psychological Causes (α=0.87)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotion State</td>
<td>.815</td>
<td>.427</td>
<td>.284</td>
</tr>
<tr>
<td>Own Behaviour</td>
<td>.766</td>
<td>.435</td>
<td>.151</td>
</tr>
<tr>
<td>Family Problems</td>
<td>.762</td>
<td>.278</td>
<td>.151</td>
</tr>
<tr>
<td>Overwork</td>
<td>.737</td>
<td>.459</td>
<td>.290</td>
</tr>
<tr>
<td>Stress or Worry</td>
<td>.727</td>
<td>.239</td>
<td>.280</td>
</tr>
<tr>
<td>Mental Attitude</td>
<td>.699</td>
<td>.481</td>
<td>.288</td>
</tr>
<tr>
<td>Diet or Eating Habits</td>
<td>.691</td>
<td>.526</td>
<td>.239</td>
</tr>
<tr>
<td><strong>Factor 2. Risk factors (α=0.80)</strong></td>
<td></td>
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</tr>
<tr>
<td>Smoking</td>
<td>.371</td>
<td>.813</td>
<td>.051</td>
</tr>
<tr>
<td>Alcohol</td>
<td>.433</td>
<td>.787</td>
<td>.145</td>
</tr>
<tr>
<td>My Personality</td>
<td>.575</td>
<td>.776</td>
<td>.259</td>
</tr>
<tr>
<td>Accident or Injury</td>
<td>.375</td>
<td>.765</td>
<td>.256</td>
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<tr>
<td>Altered Immunity</td>
<td>.180</td>
<td>.578</td>
<td>.488</td>
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<td>Ageing</td>
<td>.360</td>
<td>.558</td>
<td>.175</td>
</tr>
<tr>
<td><strong>Factor 3. External Causes (α=0.516)</strong></td>
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<tr>
<td>Germ</td>
<td>.275</td>
<td>.301</td>
<td>.764</td>
</tr>
<tr>
<td>Chance or Bad Luck</td>
<td>.164</td>
<td>.144</td>
<td>.695</td>
</tr>
<tr>
<td>Poor Past Medical Care</td>
<td>.285</td>
<td>.110</td>
<td>.598</td>
</tr>
</tbody>
</table>


7.2.4 Design and Procedure:

The study employed a cross-sectional design. Patients were approached while receiving dialysis and given relevant information as to the study requirements. After providing informed consent, patients completed the questionnaire methods while undergoing a stable HD session (see chapter 5).
7.3 Results

Two hundred and seventy-five HD patients were approached, of which 215 consented and completed the questionnaire assessments (consent rate = 78.2%). There was no significant gender difference between responders and non-responders ($X^2[1,275]=0.57$, $p=0.45$). However there was a significant difference between responders and non-responders with regards to renal centre, with a higher consent rate evident at the Lister (consent rate = 83.8%, Addenbrooke’s = 68.2%, and the Royal Free = 66.2%, $X^2[2,275]=10.4$, $p=0.005$).

Demographic and clinical data for the sample is shown in table 7.2 (n=215). The majority of the sample were male (66.5%) and white (88.4%). The average age of the sample was 60.5 (SD=15.5) years. The median dialysis vintage was 1315 days (IQR=1679). Of the 215 patients 94 reported being on the transplant waiting list, 105 not, and 16 did not know. High co-morbidity was prevalent in 61 (28.4%) of patients. The mean BDI score was 12.2 (±8.2). Sixty-four patients had a BDI ≥16 indicating potential depressive cases (29.8%).

Univariate comparisons between the depressed (BDI ≥16) and non-depressed (BDI<16) were undertaken with regards to clinical and demographic variables (table 7.2). Three variables differed between the depressed and non-depressed patients. Depressed patients were significantly younger than the non-depressed, and had significantly lower haemoglobin. Functional status as measured by the KPS was significantly lower in the depressed patients as compared to the non-depressed patients, indicating worse physical functioning in the former (table 7.2). None of the other parameters described in table 7.2 were associated with depression including gender, renal centre, marital status, transplant status, co-morbidity, CRP and albumin.
### Table: 7.2: Clinical and Demographic differences between depressed and non-depressed HD patients.

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Total</th>
<th>Depressed</th>
<th>Non-Depressed</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>143 (66.5)</td>
<td>42 (65.6)</td>
<td>101 (66.9)</td>
<td>$X^2(1,215)=0.3, p=0.85$</td>
</tr>
<tr>
<td>Female</td>
<td>72 (33.5)</td>
<td>22 (34.6)</td>
<td>50 (33.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (mean SD)</strong></td>
<td>60.5 (15.5)</td>
<td>57.0 (15.9)</td>
<td>61.9 (15.1)</td>
<td>$t(213)=2.1, p=0.034$</td>
</tr>
<tr>
<td><strong>Ethnicity n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>190 (88.4)</td>
<td>58 (90.6)</td>
<td>132 (87.4)</td>
<td>$X^2(1,215)=0.45, p=0.50$</td>
</tr>
<tr>
<td>Non-white</td>
<td>25 (11.6)</td>
<td>6 (9.4)</td>
<td>19 (12.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living with partner</td>
<td>143 (66.5)</td>
<td>39 (60.9)</td>
<td>104 (68.9)</td>
<td>$X^2(3,215)=2.9, p=0.41$</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>18 (8.4)</td>
<td>8 (12.5)</td>
<td>10 (6.6)</td>
<td></td>
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<tr>
<td>Widowed</td>
<td>23 (10.7)</td>
<td>6 (9.4)</td>
<td>17 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>31 (14.4)</td>
<td>11 (17.2)</td>
<td>20 (13.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Transplant List n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>94 (43.7)</td>
<td>29 (45.3)</td>
<td>65 (43.0)</td>
<td>$X^2(2,215)=4.0, p=0.14$</td>
</tr>
<tr>
<td>No</td>
<td>105 (48.8)</td>
<td>27 (42.2)</td>
<td>78 (51.7)</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>16 (7.4)</td>
<td>8 (12.5)</td>
<td>8 (5.3)</td>
<td></td>
</tr>
<tr>
<td><strong>KPS~</strong></td>
<td>80 (20)</td>
<td>70 (18.6)</td>
<td>80 (20)</td>
<td>$U=3500, P=0.001$</td>
</tr>
<tr>
<td><strong>Renal Centre n (%)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lister</td>
<td>155 (72.1)</td>
<td>50 (78.1)</td>
<td>105 (69.5)</td>
<td>Fisher’s Exact Test $p=0.44$</td>
</tr>
<tr>
<td>Addenbrooke’s</td>
<td>45 (20.9)</td>
<td>10 (15.6)</td>
<td>35 (23.2)</td>
<td></td>
</tr>
<tr>
<td>Royal Free</td>
<td>15 (7.0)</td>
<td>4 (6.3)</td>
<td>11 (7.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis Vintage (days)~</td>
<td>1315 (1679)</td>
<td>1390.5 (2341.3)</td>
<td>1226 (1481)</td>
<td>$U=4303, p=0.21$</td>
</tr>
<tr>
<td>Co-morbidity Group n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>76 (35.3)</td>
<td>22 (34.4)</td>
<td>54 (35.8)</td>
<td>$X^2(2,215)=0.38, p=0.83$</td>
</tr>
<tr>
<td>Moderate</td>
<td>78 (36.3)</td>
<td>22 (34.4)</td>
<td>56 (37.1)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>61 (28.4)</td>
<td>20 (31.3)</td>
<td>41 (27.2)</td>
<td></td>
</tr>
<tr>
<td>Diabetic n (%)</td>
<td>36 (16.7)</td>
<td>11 (17.2)</td>
<td>25 (16.6)</td>
<td>$X^2(1,215)=0.01, p=0.91$</td>
</tr>
<tr>
<td>Cancer n (%)</td>
<td>19 (8.8)</td>
<td>4 (6.3)</td>
<td>15 (9.9)</td>
<td>$X^2(1,215)=0.76, p=0.38$</td>
</tr>
<tr>
<td>Kt/V~</td>
<td>1.3 (0.3)</td>
<td>1.3 (0.3)</td>
<td>1.3 (0.3)</td>
<td>$t(213)=0.19, p=0.85$</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)~</td>
<td>11.4 (1.3)</td>
<td>11.1 (1.2)</td>
<td>11.6 (1.4)</td>
<td>$t(213)=2.0, p=0.043$</td>
</tr>
<tr>
<td>Albumin (g/dL)~</td>
<td>36.6 (4.1)</td>
<td>36.4 (4.4)</td>
<td>36.7 (4.0)</td>
<td>$t(123)=0.43, p=0.671$</td>
</tr>
<tr>
<td>C-Reactive Protein (mg/l)~</td>
<td>5.0 (8.0)</td>
<td>5.0 (12.6)</td>
<td>5.0 (7.6)</td>
<td>$U=4364, p=0.25$</td>
</tr>
</tbody>
</table>

Unless stated otherwise values are means and SDs. ~Median and inter-quartile Range $U=$ Mann Whitney

### 7.3.1 Description of Illness Perceptions

Mean IPQ-R scores are displayed in table 7.3. Overall HD patients held strong perceptions of the chronicity of the disease, and perceived it to have adverse consequences. Personal control perceptions appear to be stronger than treatment control perceptions. However, both treatment control and external causes had relatively low internal reliability ($\alpha$). Illness perceptions showed logical inter-correlations as presented in the correlation matrix of table 7.4. For example time-line perceptions correlated positively with consequence perceptions, coherence and emotion, and negatively with treatment and personal control. Depression
scores correlated with all the IPQ-R dimensions and negatively with functional status as measured by the KPS (table 7.4). KPS scores correlated negatively with personal control and the BDI. Inspection of the coefficients suggests that the relationship between the illness perceptions were small-moderate in effect-size.

7.3.2 Comparing illness perceptions between the depressed and non-depressed patients

Comparison of illness perceptions between depressed and non-depressed patients were sought via MANOVA (table 7.3). MANOVA with all the IPQ-R dimensions as dependent variables revealed a significant overall effect (F[11, 203]=9.1, p=0.001 η²=0.329). Depressed patients had a stronger illness identity and perception of time-line (chronicity), cyclical time-line, and negative consequences as compared to the non-depressed. Unsurprisingly depressed patients scored significantly higher on the emotion IPQ-R subscale than the non-depressed patients. Depressed patients reported lower illness coherence and treatment control. Personal control perceptions were lower in the depressed as compared to the non-depressed, a difference that was tending towards significance (p=0.06). With regards to causal perceptions, depressed patients scored significantly higher on the psychological and external factors subscales (table 7.3).

7.3.3 Comparing illness perceptions between co-morbidity groups

A MANOVA was evaluated in-order to compare illness perceptions between co-morbidity groups. MANOVA with all the IPQ-R dimensions as dependent variables revealed a non-significant overall effect (F[22, 406]=9.1, p=0.335 η²=0.057). The only illness perception that differed significantly across the co-morbidity groups was illness coherence (F(1,212) =4.4, p=0.014 η²=0.04). Post-hoc comparisons revealed that patients in the high co-morbidity group had significantly lower illness coherence scores (mean =17.3 S.E=0.53) as compared to those with medium co-morbidity (mean =19.2 S.E=0.47, p=0.01) and none-low co-morbidity (mean =19.3 S.E=0.48, p=0.008). This suggests a lower level of illness understanding for patients with severe co-morbidity.
Table 7.3: MANOVA comparisons of the illness perceptions (IQ-R) between depressed and non-depressed patients.

<table>
<thead>
<tr>
<th>IPQ-R Subscale</th>
<th>α</th>
<th>Possible Range</th>
<th>Overall</th>
<th>Depressed (n=64)</th>
<th>Non-Depressed (n=151)</th>
<th>F</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness Identity</td>
<td>0.83</td>
<td>0-14</td>
<td>5.3 (3.2)</td>
<td>6.5 (3.0)</td>
<td>4.8 (3.2)</td>
<td>13.9**</td>
<td>0.061</td>
</tr>
<tr>
<td>Timeline</td>
<td>0.83</td>
<td>6-30</td>
<td>25.4 (4.8)</td>
<td>26.6 (4.1)</td>
<td>24.9 (5.0)</td>
<td>5.3*</td>
<td>0.024</td>
</tr>
<tr>
<td>Cyclical</td>
<td>0.80</td>
<td>4-20</td>
<td>10.3 (3.5)</td>
<td>11.8 (3.4)</td>
<td>9.7 (3.4)</td>
<td>17.0**</td>
<td>0.074</td>
</tr>
<tr>
<td>Consequences</td>
<td>0.70</td>
<td>6-30</td>
<td>22.0 (4.4)</td>
<td>24.0 (3.6)</td>
<td>21.1 (4.4)</td>
<td>21.7**</td>
<td>0.093</td>
</tr>
<tr>
<td>Personal Control</td>
<td>0.78</td>
<td>5-25</td>
<td>18.1 (4.8)</td>
<td>17.1 (4.7)</td>
<td>18.5 (4.9)</td>
<td>3.8¥</td>
<td>0.018</td>
</tr>
<tr>
<td>Treatment Control</td>
<td>0.44</td>
<td>6-30</td>
<td>15.1 (3.2)</td>
<td>13.9 (3.3)</td>
<td>15.6 (3.1)</td>
<td>12.0**</td>
<td>0.053</td>
</tr>
<tr>
<td>Illness Coherence</td>
<td>0.87</td>
<td>5-25</td>
<td>18.9 (4.3)</td>
<td>17.5 (5.1)</td>
<td>19.2 (3.8)</td>
<td>7.8**</td>
<td>0.036</td>
</tr>
<tr>
<td>Emotion</td>
<td>0.86</td>
<td>6-30</td>
<td>16.2 (5.3)</td>
<td>20.4 (4.8)</td>
<td>14.4 (4.4)</td>
<td>79.2**</td>
<td>0.271</td>
</tr>
<tr>
<td>Psychological Causes</td>
<td>0.87</td>
<td>7-35</td>
<td>13.5 (5.2)</td>
<td>15.0 (6.0)</td>
<td>12.8 (4.6)</td>
<td>8.7**</td>
<td>0.039</td>
</tr>
<tr>
<td>Risk Factor Causes</td>
<td>0.80</td>
<td>6-30</td>
<td>11.0 (4.0)</td>
<td>11.7 (4.3)</td>
<td>10.7 (3.9)</td>
<td>2.5</td>
<td>0.012</td>
</tr>
<tr>
<td>External Causes</td>
<td>0.52</td>
<td>3-15</td>
<td>7.5 (2.6)</td>
<td>8.2 (2.8)</td>
<td>7.2 (2.5)</td>
<td>7.0**</td>
<td>0.032</td>
</tr>
</tbody>
</table>

**p<0.01 *p<0.05 ¥p=0.06 η²=Partial effect size α=Cronbach’s Alpha
<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>1 BDI</td>
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<tr>
<td>2 Illness Identity</td>
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</tr>
<tr>
<td>3 Timeline</td>
<td>.193**</td>
<td>.025</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>4 Cyclical</td>
<td>.309**</td>
<td>.340**</td>
<td>-.047</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>5 Consequences</td>
<td>.376**</td>
<td>.457**</td>
<td>.422**</td>
<td>.209**</td>
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<td></td>
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</tr>
<tr>
<td>6 Personal Control</td>
<td>-.176**</td>
<td>.023</td>
<td>-.213**</td>
<td>.169*</td>
<td>-.112</td>
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<tr>
<td>7 Treatment Control</td>
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<td>-.080</td>
<td>-.293**</td>
<td>.053</td>
<td>-.157*</td>
<td>.431**</td>
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<tr>
<td>8 Illness Coherence</td>
<td>-.193**</td>
<td>.051</td>
<td>.137*</td>
<td>-.199**</td>
<td>-.006</td>
<td>.065</td>
<td>-.090</td>
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<tr>
<td>9 Emotion</td>
<td>.642**</td>
<td>.354**</td>
<td>.135*</td>
<td>.428**</td>
<td>.408**</td>
<td>-.049</td>
<td>-.157*</td>
<td>-.194**</td>
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<tr>
<td>10 Psychological Causes</td>
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<td>-.018</td>
<td>-.035</td>
<td>.193**</td>
<td>-.014</td>
<td>.065</td>
<td>.009</td>
<td>-.242**</td>
<td>.250**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 Risk Causes</td>
<td>.153*</td>
<td>-.114</td>
<td>-.070</td>
<td>.086</td>
<td>-.071</td>
<td>-.042</td>
<td>-.060</td>
<td>-.292**</td>
<td>.117</td>
<td>.614**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 External Causes</td>
<td>.246**</td>
<td>.118</td>
<td>.048</td>
<td>.105</td>
<td>.055</td>
<td>.124</td>
<td>-.026</td>
<td>-.093</td>
<td>.231**</td>
<td>.358**</td>
<td>.330**</td>
<td></td>
</tr>
<tr>
<td>13 KPS</td>
<td>-.263**</td>
<td>.045</td>
<td>-.091</td>
<td>-.081</td>
<td>-.041</td>
<td>.152*</td>
<td>.074</td>
<td>.118</td>
<td>-.012</td>
<td>-.045</td>
<td>-.069</td>
<td>-.002</td>
</tr>
</tbody>
</table>

**p<0.01 *p<0.05
7.3.4 Logistic Regression: Predicting depression (BDI≥16)

Logistic regression was undertaken to identify predictors of depression (DV= BDI≥16). Demographic, clinical and psychological variables were entered into the model in a hierarchical fashion (see table 7.5). In step 1 age, gender and KPS were entered. This baseline model was significant (Chi-Square =20 df=3 p=0.001) which accounted for 12.6% of the variance estimation in depression. Functional status (β=-0.045, p=0.001) and age (β=-0.036, p=0.001) were both significant predictors of depression in this initial model. In step 2 Hb, Albumin and Kt/V were entered. Adding these clinical variables did not improve the model significantly (ΔChi-Square =3.7 df=3 p=0.3), adding only 2% to the explained variance over model 1.

In the final step the regression model improved significantly by adding all the IPQ-R items (except emotion, ΔChi-Square =53.4 df=10 p=0.01), adding a further 28% to the explained variance in depression. Emotion was not added in the model due to its highly significant relationship with depression. In this final model age (β=-0.037, p=0.014), KPS (β=-0.048, p=0.002), Hb (β=-0.31, p=0.042), treatment control (β=-0.149, p=0.03), consequences (β=0.134, p=0.02) and illness coherence (β=-0.119, p=0.014) were all significant predictors of depression. Both cyclical time-line (β=0.115, p=0.059) and psychological causes (β=0.093, p=0.07) were marginal predictors of depression. In terms of odds a one point increase in consequences increased the odds of depression by 14% (table 7.5). A one point increase in treatment control was associated with a 14% reduction in odds for depression. Furthermore, a one point increase in illness coherence was associated with an 11% decrease in the odds for depression. These results remained unchanged after including comorbidity and CRP in the model. Both of these variables were not associated with depression in any stage of the model building. The analysis was repeated with treatment control and external causes removed as both had relatively low internal consistency (α).

After doing so the results were very similar to those reported in table 7.5. The only difference was that personal control became a significant predictor of depression (β=-0.089, p=0.027) after removing treatment control. A one-point increase in personal control lead to an 8% decrease in the risk for depression (OR= 0.92 95% CI 0.85 – 0.99).
### Table 7.5: Hierarchical Logistic Regression Models. Demographic, clinical and psychological predictors of depression (BDI ≥16).

<table>
<thead>
<tr>
<th>IVs</th>
<th>Step 1 (model 1)</th>
<th>Step 2 (model 2)</th>
<th>Step 3 (model 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wald</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>10.7**</td>
<td>0.96</td>
<td>0.94-0.99</td>
</tr>
<tr>
<td>Male</td>
<td>0.37</td>
<td>1.23</td>
<td>0.63-2.41</td>
</tr>
<tr>
<td>KPS</td>
<td>14.4**</td>
<td>0.96</td>
<td>0.93-0.98</td>
</tr>
<tr>
<td>Hb</td>
<td>3.31^</td>
<td>0.80</td>
<td>0.62-1.02</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.64</td>
<td>1.03</td>
<td>0.95-1.12</td>
</tr>
<tr>
<td>Kt/V</td>
<td>0.39</td>
<td>1.46</td>
<td>0.44-4.79</td>
</tr>
<tr>
<td>Illness Identity</td>
<td>0.54</td>
<td>1.05</td>
<td>0.92-1.20</td>
</tr>
<tr>
<td>Timeline</td>
<td>0.73</td>
<td>1.04</td>
<td>0.95-1.15</td>
</tr>
<tr>
<td>Cyclical</td>
<td>3.58^</td>
<td>1.12</td>
<td>0.99-1.26</td>
</tr>
<tr>
<td>Consequences</td>
<td>5.41*</td>
<td>1.14</td>
<td>1.02-1.27</td>
</tr>
<tr>
<td>Personal Control</td>
<td>1.43</td>
<td>0.95</td>
<td>0.87-1.04</td>
</tr>
<tr>
<td>Treatment Control</td>
<td>4.67*</td>
<td>0.86</td>
<td>0.75-0.99</td>
</tr>
<tr>
<td>Illness Coherence</td>
<td>6.04**</td>
<td>0.89</td>
<td>0.81-0.98</td>
</tr>
<tr>
<td>Psychological Causes</td>
<td>3.26^</td>
<td>1.10</td>
<td>0.99-1.21</td>
</tr>
<tr>
<td>Risk Causes</td>
<td>0.45</td>
<td>0.96</td>
<td>0.84-1.09</td>
</tr>
<tr>
<td>External Causes</td>
<td>0.90</td>
<td>1.08</td>
<td>0.92-1.30</td>
</tr>
</tbody>
</table>

Chi-Square =20 df=3 p=0.001  \[ \Delta \text{Chi-Square} =3.7 \text{ df}=3 \text{ p}=0.3 \]
Nagelkerke R² = 0.126  \[ \Delta \text{Nagelkerke R²} =0.04 \text{ df}=6 \text{ p}=0.001 \]
Overall % Correct = 70.7  \[ \text{Model Chi-Square} =77.1 \text{ df}=16 \text{ p}=0.001 \]
Nagelkerke R² = 0.148  \[ \text{Nagelkerke R²} =0.428 \]
Overall % Correct = 72.1  \[ \text{Overall % Correct} =82.3 \]

**p<0.01 *p<0.05 ^p=0.07 ¥p=0.06  DV= Depressed (yes/no) OR= Odds Ratio
7.4 Discussion

In this study depression and illness representations were examined in a relatively large cross-sectional sample of established HD patients. The data here provides the first line of evidence in support of the thesis that illness representations pertaining to the CSM are associated with depression among dialysis patients. Depression was found here to be prevalent in approximately 30% of HD patients, which confirms past data (Chilcot, Wellsted, Da Silva-Gane, & Farrington, 2008; Drayer et al., 2006; Hedayati et al., 2006; Kimmel, 2002). Of course it should be borne in mind that the method of defining cases based of depression upon an adjusted BDI cut-off score is not a diagnosis of MDD. Rather this data suggests that a significant proportion of established HD patients have significant depressive symptoms.

Depressed patients had worst physical functioning as assessed by self-report than non-depressed patients, which is in accordance with data from other physical illnesses (Buchi et al., 1998; Egede, 2007; McFarlane & Brooks, 1988). Although causality cannot be inferred, depression may lead to worse disability or influence the reporting of disability. Alternatively poorer functional status may result in decreased mood. There was also a negative relationship between age and depression which supports previous findings in dialysis patients (Drayer et al., 2006; Koo et al., 2003; Lopes et al., 2002). It is speculated that younger patients may be more vulnerable to depression due to greater life disruption with regards to work and social roles. Depression was unrelated to dialysis vintage which is in accordance with past data (Hedayati et al., 2008; Kimmel & Peterson, 2005; Kimmel, Peterson et al., 1998). Others report significant associations between depression and CRP (Simic Ogrizovic et al., 2009), and between depression and albumin (Koo et al., 2003) although the data here did not support either. In addition, several studies in dialysis patients report an association between depression and co-morbidity (Hedayati et al., 2008; Lopes et al., 2002; Simic Ogrizovic et al., 2009), although findings are mixed (Drayer et al., 2006; Kimmel, Peterson et al., 1998) and the association was not supported here. Different methods of assessing both depression and extra-renal co-morbidity may underlie such contradictory findings presented within the literature. Nevertheless, the data shown here supports the first hypothesis that clinical factors add little to account for depression in established HD patients.
With regards to the second and third hypotheses; that control and consequences perceptions would be associated with depression and, in multivariate analysis illness perceptions would be the strongest predictors of affect, both were supported. Depressed patients had a more maladaptive illness representation of ESRD compared to the non-depressed reflected by a stronger illness identity, perception that ESRD is unpredictable, has adverse consequences, and is uncontrollable. Furthermore depressed patients reported greater disease-related worry, and less illness coherence (illness understanding). In logistic regression illness perceptions significantly added to the prediction of depression above and beyond clinical and demographic factors, explaining an additional 28% of the variance. Specifically, consequence, coherence, and treatment control all were independent predictors of depression. Concerns regarding the relatively low internal consistency of treatment control and risk factor causes lead to the regression being repeated with these items removed. As described earlier (chapter 5) treatment control is a complex term in ESRD due to the multifaceted treatment regimes, which may explain the relatively low internal consistency. After the removal of treatment control and causal risk factors, the findings remained largely unchanged except that personal control predicted depression. Taken together the findings demonstrate that perceiving greater disease-related consequences, and lower illness-related control and understanding (coherence) is associated with depression in HD patients. These findings also support past studies in dialysis patients that have examined illness perceptions in relation to QoL (Covic et al., 2004; Covic et al., 2006; Fowler & Baas, 2006; Griva et al., 2009; Timmers et al., 2008).

The findings described here have shown that illness perceptions are strong predictors of depression in HD patients, more so that clinical factors. Indeed these results are similar to data gathered in other illness groups (Jopson & Moss-Morris, 2003; Sharpe et al., 2001) and early data in dialysis patients (Sacks et al., 1990). Taken together it appears that the interpretation of illness is more strongly associated with mood rather than disease severity. Moreover illness perceptions appear to be largely unrelated to extra renal co-morbidity in HD patients. Illness coherence was the only perception related to co-morbidity, with lower coherence associated with increased co-morbidity. This suggests that illness understanding is reduced when individuals have several other diseases. This may be the result of more somatic symptoms and treatment requirements in highly co-morbid patients.
The thesis that illness perceptions are associated with depression is supported further by data from several disease groups (Dickens et al., 2008; Jopson & Moss-Morris, 2003; Murphy et al., 1999; Orbell et al., 1998; Schiaffino et al., 1998). For example, a study of Rheumatoid Arthritis (RA) patients revealed that depression correlated positively with consequence perceptions, and negatively with control/cure perceptions, which were upheld after controlling for disease severity (Murphy et al., 1999). Furthermore in MS patients Jopson et al (2003) revealed that lower perception of personal control, greater perceived consequences and perceptions of psychological causes predicted HADS-depression scores.

The data shown here in ESRD patients provides similar findings to these past studies suggesting that control and consequence illness perceptions are associated with depression. In addition, causal attributions have been shown to predict depression in the context of physical illness (Orbell et al., 1998; Jopson et al., 2003). Indeed, psychological causes were marginal predictors of depression in the analysis reported here suggesting that causal attributions may be important cognitions related to psychological outcomes (Roesch & Weiner, 2001; Taylor, 1983). Contrary to other empirical data illness identity (Scharloo et al., 1999) and timeline (Dickens et al., 2008) did not predict depression in the present analysis. Presumably given the chronic nature of ESRD and the reliance on 3x weekly dialysis, chronicity and identity perceptions were well defined in this sample of established HD patients.

Although this is the first study to show that illness perception are associated with depression in dialysis patients several study limitations should be considered. While the data here suggests that depression is characterised by different illness perceptions it is premature to infer causality given the cross-sectional design. There was also a bias in the recruitment of patients across the three centres, with Addenbrooke’s and the Royal Free having lower consent rates compared to the Lister. This may be because of the nature and exposure Lister patients have had to this and related research areas. Importantly depression was not associated with the location of the renal service.

Furthermore exploration of the psychological mediators underlying the established illness perception-depression relationship was not undertaken (i.e. measures of coping). Although a full evaluation of the CSM was not sought in the works of this thesis, it is unlikely that current factor analytic approaches to coping will prove overly helpful in explaining the
relationship identified in this chapter. Another limitation was a lack of information regarding previous ESRD related treatments (e.g. dialysis modalities and the number of years since ESRD diagnosis). Illness representations are conceptualised to be dynamic perceptions that operate within illness schema. These schema are likely to be complex and updated as a result of previous dialysis history, transplantation and years with CKD. Further studies should consider factors relating to past dialysis and CKD histories.

7.5 Concluding remarks

In a cross-section sample of HD patients the thesis that illness representations would predict depression was supported. The findings underline the importance of understanding the nature and content of illness perceptions in relation to psychosocial outcomes, particularly as psychological interventions aimed at improving maladaptive illness perceptions improve outcomes (Broadbent et al., 2009; Petrie et al., 2002). Significantly these findings highlight that it is not the disease per se that decreases mood, rather it is the interpretation and regulation of the disease that appears to be more salient.

The following chapter extends this work by examining the longitudinal relationship between depression and illness perceptions in an incident cohort of dialysis patients over the first year of dialysis therapy.
Chapter 8
A Longitudinal Evaluation of Depression and Illness Representations in incident dialysis patients

8.1 Introduction
The cross-sectional study presented in the previous chapter supports the thesis that illness perceptions and depression are associated in established haemodialysis patients. Moreover it appears that clinical variables including co-morbidity explain little variation in depression. Rather it is an individual’s representation and regulation of the disease that is associated with depressive symptoms. The present chapter builds upon this cross-sectional work by examining the relationship between illness representations and depression over the first year of dialysis in a sample of incident dialysis patients. Studying incident dialysis patients has several advantages in this regard;

1) It is presumed that the first year of treatment represents a period of adaption, thus a platform from which to study the self-regulation of illness through illness representations. That is, illness representations are expected to alter over time according to continued self-regulation.

2) Patients start dialysis via different “paths”; some after receiving dialysis education and work-up (i.e. a progressive deterioration in renal function- termed planned starters), and others who start suddenly (for example acute presenters - termed unplanned starters). It is assumed that there will be different interpretations (i.e. representations) of illness during this period depending on how individuals start their therapy (unplanned vs. planned start).

As suggested by the evidence presented in chapter 7 and from elsewhere within the literature, depression and illness representations are closely associated. It is therefore hypothesised that starting dialysis via a particular route (e.g. an unplanned start) would involve different illness representations that may serve as vulnerabilities for depression. Therefore the study of incident patients allows a dynamic model between illness
representations and depression to be assessed over time using variations of Structural Equation Modelling (SEM). The overarching aim of this chapter is to describe illness representations in incident dialysis patients and their relationship with the trajectory of depression symptoms over the first year of therapy.

8.8.1 Depression in ESRD: initiation and time course

As reviewed in chapter 2 depression is a common issue among ESRD patients, with many studies examining the point prevalence of the disorder, using either diagnostic approaches or screening tools. While cross-sectional studies are useful in this regard and allow associations with psychological and clinical factors to be established, they suffer in that they cannot make temporal associations nor can they assess the variability of depression (i.e. change) and the associated antecedents. There is little data describing the extent of depressive symptoms and impairments in health related quality of life soon after dialysis initiation (Korevaar et al., 2000; Merkus et al., 1997). Nevertheless some US data suggests a relatively high level of depression symptoms following the initiation of dialysis therapy, with 44% scoring ≥15 on the BDI (Watnick et al., 2003). A larger study of incident patients report a similar prevalence, with 45% screening positive for depression on a three item measure derived from the diagnostic interview schedule (Walters et al., 2002). Walters et al (2002) report that depressed patients had lower health related quality of life compared with the non-depressed, yet the two groups did not differ significantly on demographic or clinical variables including co-morbidity. Given this, one intriguing question is whether there is anything inherent in the manner in which individuals start dialysis that increases the vulnerability to depression. In a small study Miura et al (1999) assessed depression symptoms before and after dialysis initiation comparing those with a planned start, to those who started unplanned. The results indicated that both before and after dialysis introduction, patients with an unplanned start had greater depression symptoms as assessed by the Zung self-rating depression scale, compared to those with a planned start. This study albeit very small and largely uncontrolled, suggests that unplanned dialysis initiation is associated with more depressive symptoms as compared to planned initiation.

Others have assessed the timing of dialysis initiation (when to put a patient onto dialysis) according to opinion based guidelines (KDOQI) in relation to health related QoL (Korevaar et
al., 2002). Patients were defined as timely dialysis starters or untimely dialysis starters based upon the level of urea clearance ($Kt/V_{urea}$) and normalised protein catabolic rate (nPCR), which is a measure of protein nutritional adequacy based on urea kinetic modelling. Patients who had a timely start to dialysis according to the guidelines had greater perceived health related QoL at baseline compared to untimely starters on several components of the SF-36. However over a 12 month follow-up differences between the two groups disappeared suggesting the timing of dialysis initiation upon QoL is transient and only observed during the first few months of dialysis therapy. Interestingly timely and untimely starters did not differ significantly at baseline, or over time on mental health scores of the SF-36. This evidence supports the argument presented earlier that clinical factors are not strong associates of psychological distress among dialysis patients.

As for longitudinal data describing the course of depression over time, there remain few examples in the ESRD population. A longitudinal study of HD patients reports a 29% prevalence rate for depressive disorder using the SCID at baseline assessment (Cukor et al., 2008). Interestingly, 43% of patients diagnosed with depressive disorder at baseline still satisfied the criteria 16 months later. A persistent depressive course was associated with reduced perceived health status and quality of life and a depressive history (Cukor et al., 2008). Although of interest, this study fails to evaluate the variability of change over time and only employed a two-wave design. A larger study of incident patients reports that the mental health component scores of the SF-36 improved significantly over the first year of dialysis therapy (Korevaar et al., 2002). Although depression symptoms were not directly evaluated (i.e. via the BDI or HADS), the merits of this study include an appropriate design (i.e. several time points) and use of multi-level modelling. Evidently there is a paucity of longitudinal data, and the trajectory of depression over the dialysis career remains undefined.

8.8.2 Illness Perceptions over time and their association with depression

As reviewed in chapter 3 there is good evidence that illness perceptions predict an array of outcomes in functional status, quality of life and depression. Indeed, a key tenet of self-regulation is that individuals consistently monitor and adapt behaviours in order to obtain particular goals. According to the CSM illness perceptions provide the interpretation of the
illness threat and inform coping procedures (via “IF-THEN rules) in an attempt to control the threat (Leventhal et al., 2003; Leventhal et al., 1992). Given the dynamic nature of the CSM, illness perceptions may be expected to change over time as individuals self-regulate. Remarkably however, few data are available that describe the change in illness perceptions over time. Longitudinal data from chronic illness groups including cardiac diseases (Sheldrick et al., 2006), diabetes (Lawson et al., 2008) and osteoarthritis (Bijsterbosch et al., 2009; Kaptein et al., 2010) suggest that timeline and illness coherence perceptions increase with time, whereas controllability perceptions and emotional representations decrease over time. It has also been demonstrated that changes in illness perceptions predict clinical (Bijsterbosch et al., 2009; Kaptein et al., 2010) and psychological outcomes (Sheldrick et al., 2006). However others report relative stability in illness perceptions over time in patients with lower back pain (Foster et al., 2008) and irritable bowel syndrome (Rutter & Rutter, 2007), although the later study of Rutter and Rutter was most probably underpowered.

Illness perceptions as predictors of later depression have been reported in some studies, yet there are vast differences in designs and statistical approaches to the analysis. As previously described (chapter 3) Schiaffino et al (1998) reported that illness perceptions predict the change in depression over time in RA and MS patients. In RA patients both curability and personal responsibility perceptions predicted later depression, whereas a stronger perception that symptoms varied from day to day was predictive of depression in the MS sample. Similarly, control perceptions predicted post-operative depression in patients who received a surgical intervention for osteoarthritis (Orbell et al., 1998). Dickens et al (2008) provides additional evidence revealing that time-line and control perceptions predict new-onset depression following a MI. While most data is supportive of illness perceptions predicting depression at a later point in time, few have utilised more advanced statistical approaches like growth or multilevel models. Lane et al (2009) found no support that illness perceptions predicted the trajectory of depression in patients with atrial fibrillation using growth modelling. In ESRD only one study has examined illness perceptions over time together with changes in health related quality of life (Covic et al., 2006). Covic et al (2006) followed HD patients over two years and reported that emotional representations reduced over time, whereas illness coherence and perceptions of treatment control increased. Moreover baseline illness representations predicted improvements in QoL. Higher personal
control and illness coherence, and lower emotion representations at time one predicted improved physical QoL scores at time 2. Lower baseline consequence scores were associated with improvements in mental QoL functioning. Despite the relatively small sample size, only two time points, and a lack of consideration of extra-renal co-morbidity, these results suggest that illness representations are dynamic and are associated with changes in QoL in HD patients.

While data corroborate the utility of the CSM by showing that illness perception are associated with depression in other illness groups, and may be associated with the change in depression over time, no study has explored their longitudinal associations in ESRD. Therefore this study set out to examine the following hypothesis and defend the thesis that illness perceptions and depression share a longitudinal relationship.

**Baseline Hypotheses:**

1) Patients with an unplanned path to dialysis have different illness perceptions and more depressive symptoms compared to planned patients.

2) Illness perceptions predict depression. Path to dialysis has an indirect effect upon depression mediated by illness perceptions. Clinical and demographic factors are largely unrelated to depression.

**Longitudinal Hypotheses:**

3) Depression symptoms decrease over time.

4) Patients self-regulate, evidenced by a change in illness perceptions over time, although given the nature of ESRD changes may be relatively small.

5) Illness perceptions predict the change in depression over time.
8.2 Methods

8.3.1 Patients

An incident cohort of dialysis patients from three UK renal centres were approached and recruited during the period of May 2007- May 2009. All patients were recruited within 3 months of dialysis initiation. Patients were approached providing they met the following criteria; i) started in-centre HD or PD within last 3 months, ii) no previous dialysis history, iii) no known significant visual or physical impairment that would prevent the completion of the questionnaires, iv) fluency in verbal and written English language, (v) not hospitalised at the time of assessment and vi) no cognitive impairment as indicated by an age adjusted score of <22 on the Mini Mental State Examination (Folstein et al., 1975).

8.3.2 Materials

Demographic questionnaire: Information on age, gender, ethnicity, marital-status, and work-status were collected by means of a patient questionnaire. Transplant status was determined via self-report. Patients were asked if they were currently on the transplant waiting list (yes, no or don’t know). Smoking status was ascertained via self-report.

The Revised Illness Perception Questionnaire (IPQ-R): As described in chapter 4. The sample size permitted Principle Component Analysis on the 18 causal items of the IPQ-R as recommended by (Moss-Morris et al., 2002). The three causal items identified in the previous chapters were employed here.

Depression Symptoms: Depression symptoms were assessed via the Beck Depression Inventory (BDI-II) as described in Chapter 4. A BDI≥16 was employed to define patients with probable depression (see chapter 5). The BDI was treated as a categorical outcome (i.e. BDI≥16) to evaluate differences between depressed and non-depressed patients. Given that the aim was to examine the change in depression symptoms over time, the BDI was also treated as a continuous variable in the Structure Equation Modelling that follows (i.e. a BDI total score). As described in chapter 6 the total BDI scores provides a good overall measure of depressive affect encompassing general, cognitive and somatic symptoms.
8.3.3 Clinical Data

Functional Status and Comorbidity: Karnofsky Performance Score was employed to assess functional status (see chapter 4). Comorbidity was assessed using a semi-quantitative technique (Chandna et al., 1999), scored by consultant nephrologist who assigned a severity score for each patient (1= no co-morbidity, 2= mild moderate co-morbidity, 3= severe co-morbidity. A similar method described by Davies et al was also employed. Both methods have been described previously in the general methods (see chapter 4).

Clinical parameters: Routine haematological and biochemical parameters collected as a part of the routine care of patients within the service were recorded. These included Haemoglobin, Albumin, CRP and sessional dialysis Kt/V. In addition primary ESRD diagnosis was recorded from medical notes. Estimated GFR was calculated from serum creatinine concentrations at the time of dialysis initiation, using the modified MDRD equation below (Levey et al., 1999).

\[
\text{eGFR (ml/min/1.73m}^2) = 186 \times \text{[Serum Creatinine]}^{-1.154} \times \text{[Age]}^{-0.203} \times \text{[0.742 if female]} \times \text{[1.21 if black]}
\]

Depressive History: Depressive history was recorded, where depressive disorders were listed in the medical problem lists in patients’ medical record. Anti-depressant use at the time of assessment was also recorded.

Path to dialysis: Planned starters were defined as those with known Stage V CKD who saw a nephrologist at least once within 90 days pre-initiation. Unplanned starters were those who had no contact with a nephrologist within 90 days pre-dialysis, including some who may have been seen before this 90 day period. This definition is defined and implemented in the UK renal registry.
8.3.4 Design and Procedure

A three-wave panel design was employed in this study. Patients were recruited at a point soon after dialysis initiation (within three months of initiation, \( t_1 \)) and assessed 6 (\( t_2 \)) and 12 months (\( t_3 \)) thereafter.

Eligible HD patients were approached while on-dialysis, whereas eligible PD patients were approached via phone or whilst in clinic. HD patients completed the measures while on dialysis (chapter 5), while PD patients completed the measures during a routine clinic appoint or were sent the questionnaires in the post. Clinical data as described above were collected from electronic medical records.

8.3.5 Statistical Methods

The results presented in the following section are separated into two parts. Part one describes the baseline data and addresses the first two hypotheses (1-2) described in the introduction. The second part concerned the longitudinal data thus addressed the longitudinal hypotheses (3-5) as described above.

In order to examine the baseline hypotheses SEM was employed to examine the cross-sectional association between path to dialysis, illness perceptions and depression. Before examining the structural relations between these variables a measurement model for the IPQ-R was defined, the data from which is presented in the results. The SEM was defined based upon the assumption that path to dialysis would influence patients illness perceptions. Further, illness perceptions were hypothesised to be associated with depression in accordance with the data presented in the preceding chapter.

Model fit was assessed via examination of the chi-square statistic and fit indices, specifically the CFI, TLI and RMSEA (see general methods). To reiterate, a CFI=0.95, TLI=0.95 and RMSEA=0.05 each suggest adequate fit to the data. Model trimming was attempted by removing non-significant regression paths from the SEM with the model then re-evaluated. The DIFFTEST\(^{10} \) in Mplus was used to test whether the original and the trimmed (i.e. nested model) differed significantly. A non-significant chi-square between the two models

\(^{10} \) The difference in chi-square between two nested models when the estimator is WLSMV cannot be determined by the convention chi-square difference test. In Mplus the DIFFTEST can be used in such cases (mean-adjusted robust chi-square test).
demonstrates that the two models (original vs. nested) do not differ significantly with regards to their relative fit.

In the second part of the analysis the trajectories (i.e. mean change and the variance of the change) for depression and illness perceptions were assessed using Latent Growth Models (LGM). For each model the loads of the intercept factor (i.e. baseline starting value) were constrained to 1. The loadings on the slope (i.e. the change factor) were set at 0 at the baseline ($t_1$), 0.5 at the 6 month follow-up ($t_2$) and 1 at the 12 month follow-up ($t_3$). Loading the slopes in this manner implies a linear change over time.

In addition to the linear latent growth model, an unspecified latent growth model for depression was also evaluated since the function of the trajectory was not known. In this unspecified model two of the slopes were fixed to be 0 ($t_1$) and 0.5 ($t_2$), with the final slope loading ($t_3$) freed to be estimated in the model. Therefore the co-efficient of the final slope is statistically estimated from the data.

Finally, predictors of the trajectory (linear change) of depression over one year were sought in latent growth models, where the intercept and slopes were regressed upon independent variables (illness perceptions). Initially the predictability of each illness perception (subscale scores) upon the trajectory of depression were evaluated in separate growth models in order to retain power. Perceptions that predicted the trajectory of depression were then entered into a combined model controlling for the effects of each of the selected perception variables.
8.3 Results Part I: Analysis of Baseline Data

8.3.1 Patient characteristics

Two hundred and twenty one initiating dialysis patients who were eligible for study were approached. One hundred and sixty patients gave consent and completed the baseline measures (consent rate =72.4%). The median dialysis vintage at baseline was 30.5 days (min 1- max 100, IQR =35.8). Participants (n=160) and non-participants (n=61) did not differ significantly with regards to their age (t[219]=0.19,p=0.233], sex (X²[1,221]=1.62, p=0.20), treatment modality (X²[1,221]=0.99, p=0.32), or renal service. (X²[2,221]=4.4, p=0.11). A summary of patient attrition over the study period is presented in figure 8.1. Of the 160 patients recruited at baseline, 133 were still on dialysis at the 6 month assessment, with 106 dialysing at 12 months. Patients who remained on dialysis (completers n=106) were compared with patients would did not complete the study (non-completers n=27, excluding patients who died or were transplanted). There was no association between the renal service and non-completion (X²[2,221]=1.5, p=0.48), nor was there any gender difference between completers and non-completers (X²[1,221]=0.05, p=0.83). In addition completers and non-completers did not differ significantly with regards to age (t[219]=0.19,p=0.233]. However non-completers did have significantly higher baseline BDI scores (mean =15.9 ±10.8) as compared to completers (mean =10.4 ±7.2, t[32.2]=2.5, p=0.02). Furthermore there was a significant association between non-completion and treatment modality with all PD patients completing (n=24, 100%), versus 82 (72.2%) of HD patients (X²[1,221]=7.5, p=0.006).

A summary of clinical and demographic characteristics at baseline (n=160) is presented in table 8.1. The mean age of the sample was 54.7 (±16.0). The majority of patients were male (67.5%), white (90.6%) and on HD (82.5%). Unplanned dialysis initiation occurred in 45 patients (28.1%). A positive depressive history was noted in 24 patients (15%). At baseline forty-one patients (25.6%) scored ≥16 on the BDI suggesting possible depression.

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11 Excluding deaths and transplantation
8.3.2 Differences between depressed and non-depressed patients at baseline

Baseline differences between the depressed and non-depressed patients with regards to clinical and demographic factors are displayed in table 8.1. Depressed patients were significantly younger than the non-depressed and had better physical functioning.
Table 8.1: Demographic and clinical data at baseline: Comparisons between the depressed (BDI≥16) and non-depressed (BDI<16) patients.

<table>
<thead>
<tr>
<th></th>
<th>Overall n=160</th>
<th>Depressed n=41</th>
<th>Non-depressed n=119</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean SD)</strong></td>
<td>57.4 (16.0)</td>
<td>53.2 (14.3)</td>
<td>58.8 (16.3)</td>
<td>t(158)=1.95, p=0.05</td>
</tr>
<tr>
<td><strong>Gender (male n, %)</strong></td>
<td>108 (67.5%)</td>
<td>25 (61%)</td>
<td>83 (69.7%)</td>
<td>X²(1,160)=1.07, p=0.301</td>
</tr>
<tr>
<td><strong>Ethnicity (white n, %)</strong></td>
<td>145 (90.6%)</td>
<td>35 (85.4%)</td>
<td>110 (92.4%)</td>
<td>Fisher’s Exact Test, p=0.215</td>
</tr>
<tr>
<td><strong>Marital Status (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/Living with Partner</td>
<td>106 (66.3%)</td>
<td>27 (65.9%)</td>
<td>79 (66.4%)</td>
<td>X²(1,160)=0.04, p=0.95</td>
</tr>
<tr>
<td>Single/Widowed</td>
<td>54 (33.7%)</td>
<td>14 (34.1%)</td>
<td>40 (33.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Path to dialysis (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned</td>
<td>115 (71.9%)</td>
<td>22 (53.7%)</td>
<td>93 (78.2%)</td>
<td>X²(1,160)=9.05, p=0.003</td>
</tr>
<tr>
<td>Unplanned</td>
<td>45 (28.1%)</td>
<td>19 (46.3%)</td>
<td>26 (21.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Dialysis Vintage (days)</strong></td>
<td></td>
<td></td>
<td></td>
<td>t(158)=0.68, p=0.498</td>
</tr>
<tr>
<td></td>
<td>38.6 (26.7)</td>
<td>41.0 (28.4)</td>
<td>37.8 (26.2)</td>
<td></td>
</tr>
<tr>
<td><strong>KPS&lt;70 (dependent n, %)</strong></td>
<td></td>
<td></td>
<td></td>
<td>X²(1,160)=20.2, p&lt;0.001</td>
</tr>
<tr>
<td><strong>Diagnosis (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncertain aetiology</td>
<td>29 (18.1%)</td>
<td>7 (17%)</td>
<td>22 (18.5%)</td>
<td>Fisher’s Exact Test, p=0.757</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>21 (13.1%)</td>
<td>6 (14.6%)</td>
<td>15 (12.6%)</td>
<td></td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>6 (3.8%)</td>
<td>2 (4.9%)</td>
<td>4 (3.4%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>27 (16.9%)</td>
<td>6 (14.6%)</td>
<td>21 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>Polycystic kidney</td>
<td>19 (11.9%)</td>
<td>2 (4.9%)</td>
<td>17 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (8.7%)</td>
<td>4 (9.8%)</td>
<td>10 (8.4%)</td>
<td></td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>8 (5%)</td>
<td>2 (4.9%)</td>
<td>6 (5%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>36 (22.5%)</td>
<td>12 (29.3%)</td>
<td>24 (20.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment (HD n, %)</strong></td>
<td>132 (82.5%)</td>
<td>34 (82.9%)</td>
<td>98 (82.4%)</td>
<td>X²(1,160)=0.07, p=0.934</td>
</tr>
<tr>
<td><strong>Smoker (n, %)</strong></td>
<td>57 (35.6%)</td>
<td>14 (34.1%)</td>
<td>43 (36.1%)</td>
<td>X²(1,160)=0.053, p=0.819</td>
</tr>
<tr>
<td><strong>Mod-High-comorbidity (n, %)</strong></td>
<td>58 (36.3%)</td>
<td>16 (39%)</td>
<td>42 (35.3%)</td>
<td>X²(1,160)=0.184, p=0.668</td>
</tr>
<tr>
<td><strong>Diabetic (n, %)</strong></td>
<td>39 (24.4%)</td>
<td>10 (24.4%)</td>
<td>29 (24.4%)</td>
<td>X²(1,160)=0.01, p=0.998</td>
</tr>
<tr>
<td><strong>Positive depressive history (n, %)</strong></td>
<td>24 (15%)</td>
<td>10 (24.4%)</td>
<td>14 (11.8%)</td>
<td>X²(1,160)=3.81, p=0.05</td>
</tr>
<tr>
<td><strong>Hb (g/dL mean SD)</strong></td>
<td>10.3 (1.9)</td>
<td>10.5 (1.8)</td>
<td>10.3 (1.9)</td>
<td>t(158)=0.79, p=0.431</td>
</tr>
<tr>
<td><strong>Albumin (g/l mean SD)</strong></td>
<td>35.6 (5.4)</td>
<td>34.6 (6.2)</td>
<td>36.0 (5.1)</td>
<td>t(158)=1.43, p=0.153</td>
</tr>
<tr>
<td>**CRP (mg/l)**a</td>
<td>7.0 (14.0)</td>
<td>8.0 (14.3)</td>
<td>6.0 (14.0)</td>
<td>U=2341, p=0.698</td>
</tr>
<tr>
<td><strong>eGFR (ml/min)b</strong></td>
<td>8.9 (3.3)</td>
<td>8.8 (3.8)</td>
<td>8.9 (3.1)</td>
<td>t(158)=0.152, p=0.879</td>
</tr>
</tbody>
</table>

a-Median and inter-quartile range  
b-eGFR according to the MDRD equation U= Mann Whitney U.
Depressed patients were also more likely to have a positive history of depression (OR= 2.4, 95% CI 1.0-5.9, p<0.05) as compared to the non-depressed patients. In addition depressed patients were significantly more likely to have an unplanned start to dialysis (OR=3.1, 95% CI 1.5-6.6, p<0.05) as compared to the non-depressed. As found previously in chapter 7, depression was not associated significantly with the remaining variables displayed in table 8.1 including, treatment modality, gender, renal diagnosis, albumin, CRP, eGFR and co-morbidity.

The mean BDI scores across the co-morbidity groups (low [n=66], medium [n=36], and high [n=58] were 12.2 (±8.4), 11.4 (±10.9) and 12.7 (±7.4) respectively. ANOVA revealed the BDI scores did not vary significantly across the co-morbidity groups (F[2,159]=0.27, p=0.78). These null findings were confirmed after coding co-morbidity according to the Davies et al (2002) method (F[2,159]=2.5, p=0.10).

Comparisons of illness perceptions between depressed and non-depressed patients were sought via MANOVA (table 8.2). MANOVA with all the IPQ-R dimensions as dependent variables revealed a significant overall effect (F[11, 148]=7.1, p=0.001 η²=0.347). Depressed patients had a stronger illness identity and cyclical time-line perceptions, greater perceived negative consequences, and lower illness coherence as compared to the non-depressed. Unsurprisingly depressed patients scored significantly higher on the emotion IPQ-R subscale than the non-depressed patients. With regards to causal perceptions, depressed patients scored significantly higher on the psychological subscale compared to the non-depressed.
Table 8.2: Comparison of illness perceptions between depressed and non-depressed patients.

<table>
<thead>
<tr>
<th>IPQ-R Subscale</th>
<th>Mean (SD)</th>
<th>MANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Depressed (n=41)</td>
</tr>
<tr>
<td>Illness Identity</td>
<td>4.6 (2.8)</td>
<td>5.6 (3.1)</td>
</tr>
<tr>
<td>Timeline</td>
<td>24.3 (4.2)</td>
<td>23.8 (4.6)</td>
</tr>
<tr>
<td>Cyclical</td>
<td>10.4 (3.4)</td>
<td>11.3 (3.7)</td>
</tr>
<tr>
<td>Consequences</td>
<td>21.8 (4.0)</td>
<td>24.1 (3.5)</td>
</tr>
<tr>
<td>Personal Control</td>
<td>20.3 (4.4)</td>
<td>20.1 (4.8)</td>
</tr>
<tr>
<td>Treatment Control</td>
<td>16.7 (3.2)</td>
<td>16.2 (3.3)</td>
</tr>
<tr>
<td>Illness Coherence</td>
<td>17.4 (4.6)</td>
<td>15.6 (4.7)</td>
</tr>
<tr>
<td>Emotion</td>
<td>17.3 (5.3)</td>
<td>22.3 (4.9)</td>
</tr>
<tr>
<td>Psychological Causes</td>
<td>14.2 (5.1)</td>
<td>15.8 (5.9)</td>
</tr>
<tr>
<td>Risk Factor Causes</td>
<td>11.4 (4.0)</td>
<td>11.7 (4.6)</td>
</tr>
<tr>
<td>External Causes</td>
<td>7.1 (2.1)</td>
<td>7.5 (2.2)</td>
</tr>
</tbody>
</table>

**p<0.01 *p<0.05 η²= Partial effect size. Values shown are means and standard deviations.

8.3.3 Correlates of depression scores at baseline

Correlations between the BDI with demographic, clinical and illness perception data were sought. The BDI correlated significantly with age \((r=-0.299, p=0.04)\) and functional performance (Spearman’s rho =-0.435, \(p=0.001\)). The BDI failed to correlate with albumin \((r=-0.092, p=0.248)\), Haemoglobin \((r=-0.04, p=0.645)\), CRP (Spearman’s rho =0.06, \(p=0.445\)), dialysis vintage \((r=0.05, p=0.573)\) and eGFR \((r=0.08, p=0.328)\). The BDI correlated significantly with several IPQ-R dimensions: identity \((r=0.375, p=0.001)\), cyclical-timeline \((r=0.291, p=0.001)\), consequences \((r=0.411, p=0.001)\), coherence \((r=-0.267, p=0.001)\), emotion \((r=0.673, p=0.0001)\), psychological causes \((r=0.195, p=0.014)\) and external causes \((r=0.174, p=0.028)\).
8.3.4 Differences between unplanned and planned patients at baseline.

Unplanned and planned starters did not differ at baseline with regards to the following variables: age, gender, renal centre, co-morbidity, eGFR, depressive history and dialysis vintage (data not presented). However unplanned patients had significantly lower albumin (mean=33.7 ±5.9) as compared to planned patients (mean =36.4 ±5.0, t[158]=2.8, p=0.005). In addition haemoglobin was significantly lower in the unplanned group (mean =9.4 ±2.0) as compared to planned group (mean 10.7 ±1.7, t[158]=4.0, p=0.0001).

As noted above unplanned entry was associated with a greater portion of BDI scores ≥16 as compared to planned entry. In addition mean BDI scores in unplanned starters were significantly higher than planned starters (15.6 ±8.5 vs. 10.9±8.4, t[158]=3.17, p=0.002). Comparison of the groups with regards to their illness perceptions at baseline was evaluated in MANOVA (see table 8.4 for means and 95% CIs). MANOVA revealed a significant overall effect between the groups (F[11,148]=3.1, p=0.001 η²=0.190). Specifically unplanned starters had significantly lower time-line perceptions (F[1,158]=5.8, p=0.017 η²=0.035), greater perceptions of cyclicity (F[1,158]=11.1, p=0.001 η²=0.065), greater perceptions of adverse consequences (F[1,158]=4.4, p=0.038 η²=0.027), a greater emotional response (F[1,158]=7.8, p=0.006 η²=0.047) and lower illness coherence (F[1,158]=14.1, p=0.001 η²=0.082), as compared to the planned starts. With regards to the causal items, unplanned starters had stronger perceptions of external (F[1,158]=6.1, p=0.014 η²=0.038) and psychological causes (F[1,158]=7.8, p=0.006 η²=0.047).

8.3.5 Difference between treatment modality at baseline

HD and PD patients had comparable mean BDI scores at baseline (12.2 ±8.8 vs. 12.3 ±8.1 respectively t[158]=0.63, p=0.95). MANOVA revealed a non-significant overall effect between the treatment groups with regards to illness perceptions (F[11,148]=1.8, p=0.056 η²=0.119). Only two individual perceptions appeared to differ between the groups. As compared to HD patients, PD patients had greater illness identity (5.8±2.4 vs. 4.4±2.9 F[11,148]=5.7, p=0.018 η²=0.035) and greater illness coherence (20.1±4.0 vs. 16.9±4.5 F[11,148]=12.5, p=0.001 η²=0.073).
8.3.6 Structural Equation Model: Defining a measurement model for illness perceptions (IPQ-R)

A measurement model for six illness perceptions (illness identity, cyclical timeline, illness coherence, perceived consequences, psychological causes and external causes) was evaluated in Confirmatory Factor Analysis. These perceptions were selected for inclusion in the measurement due to their cross-sectional relationship with depression as determined in univariate analysis. Baseline emotion scores were not included in the measurement model due to a high correlation with baseline depression scores. Since emotion would not be included in the structural models that follow, it was decided to evaluate the measurement model without these items. Missing data on the IPQ-R and BDI was small and replaced with median scores of the item. Since the subscales on the IPQ-R are treated on an ordinal scale, and illness identity comprised of summing the number of symptoms attributed to ESRD, WLSMV estimation was employed which is used when data is either categorical or ordinal. Three items in the illness identity were not included in the model because very few patients reported these symptoms (sore throat, sore eyes, and wheeziness).

The model parameterisation is depicted in table 8.3 accompanied by the standardised model estimates, variance explained and residual variance (error). Model fit as evaluated by chi-Square suggested poor fit ($X^2=142.7 \text{ df}=70, p<0.001$), however as described in the general methods and chapter 6 the chi-square statistic is sensitive to sample size (Ullman, 2006) thus several fit indices were evaluated. The fit indices suggested that the measurement model had adequate fit ($\text{CFI}= 0.96$, $\text{TLI}= 0.96$, $\text{RMSEA}=0.08$). This IPQ-R measurements model was therefore utilised in a structural model evaluated below.
Table 8.3: A confirmatory factor analysis of selected illness perceptions (IPQ-R).

<table>
<thead>
<tr>
<th>Item</th>
<th>Description of item</th>
<th>Factor</th>
<th>Loading</th>
<th>$R^2$</th>
<th>Residual Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID1</td>
<td>Pain</td>
<td>IDENTITY</td>
<td>0.674</td>
<td>0.455</td>
<td>0.545</td>
</tr>
<tr>
<td>ID2</td>
<td>Sore Throat</td>
<td>IDENTITY</td>
<td>0.800</td>
<td>0.640</td>
<td>0.360</td>
</tr>
<tr>
<td>ID4</td>
<td>Breathlessness</td>
<td>IDENTITY</td>
<td>0.444</td>
<td>0.198</td>
<td>0.802</td>
</tr>
<tr>
<td>ID5</td>
<td>Weight Loss</td>
<td>IDENTITY</td>
<td>0.357</td>
<td>0.127</td>
<td>0.873</td>
</tr>
<tr>
<td>ID6</td>
<td>Fatigue</td>
<td>IDENTITY</td>
<td>0.663</td>
<td>0.440</td>
<td>0.560</td>
</tr>
<tr>
<td>ID7</td>
<td>Stiff Joints</td>
<td>IDENTITY</td>
<td>0.800</td>
<td>0.640</td>
<td>0.360</td>
</tr>
<tr>
<td>ID10</td>
<td>Headaches</td>
<td>IDENTITY</td>
<td>0.475</td>
<td>0.226</td>
<td>0.774</td>
</tr>
<tr>
<td>ID11</td>
<td>Upset Stomach</td>
<td>IDENTITY</td>
<td>0.666</td>
<td>0.444</td>
<td>0.556</td>
</tr>
<tr>
<td>ID12</td>
<td>Sleep Difficulties</td>
<td>IDENTITY</td>
<td>0.558</td>
<td>0.312</td>
<td>0.688</td>
</tr>
<tr>
<td>ID13</td>
<td>Dizziness</td>
<td>IDENTITY</td>
<td>0.586</td>
<td>0.343</td>
<td>0.657</td>
</tr>
<tr>
<td>ID14</td>
<td>Loss of Strength</td>
<td>IDENTITY</td>
<td>0.674</td>
<td>0.454</td>
<td>0.546</td>
</tr>
<tr>
<td>IP6</td>
<td>My kidney problem is serious</td>
<td>CONSEQUENCES</td>
<td>0.773</td>
<td>0.597</td>
<td>0.403</td>
</tr>
<tr>
<td>IP7</td>
<td>Major Consequences on life</td>
<td>CONSEQUENCES</td>
<td>0.829</td>
<td>0.687</td>
<td>0.313</td>
</tr>
<tr>
<td>IP8</td>
<td>Does not have much effect</td>
<td>CONSEQUENCES</td>
<td>0.539</td>
<td>0.290</td>
<td>0.710</td>
</tr>
<tr>
<td>IP9</td>
<td>Affects the way others see me</td>
<td>CONSEQUENCES</td>
<td>0.567</td>
<td>0.322</td>
<td>0.678</td>
</tr>
<tr>
<td>IP10</td>
<td>Financial consequences</td>
<td>CONSEQUENCES</td>
<td>0.576</td>
<td>0.332</td>
<td>0.668</td>
</tr>
<tr>
<td>IP11</td>
<td>Difficulties for those who are close</td>
<td>CONSEQUENCES</td>
<td>0.553</td>
<td>0.306</td>
<td>0.694</td>
</tr>
<tr>
<td>IP24</td>
<td>Symptoms are puzzling</td>
<td>COHERENCE</td>
<td>0.891</td>
<td>0.794</td>
<td>0.206</td>
</tr>
<tr>
<td>IP25</td>
<td>Kidney problem is a mystery</td>
<td>COHERENCE</td>
<td>0.923</td>
<td>0.852</td>
<td>0.148</td>
</tr>
<tr>
<td>IP26</td>
<td>Don’t understand my kidney problem</td>
<td>COHERENCE</td>
<td>0.909</td>
<td>0.826</td>
<td>0.174</td>
</tr>
<tr>
<td>IP27</td>
<td>Kidney problem doesn’t make sense</td>
<td>COHERENCE</td>
<td>0.881</td>
<td>0.776</td>
<td>0.224</td>
</tr>
<tr>
<td>IP28</td>
<td>I have a clear picture/understanding of my condition</td>
<td>COHERENCE</td>
<td>0.542</td>
<td>0.294</td>
<td>0.706</td>
</tr>
<tr>
<td>IP29</td>
<td>Symptoms change day to day</td>
<td>CYCLICAL TIME</td>
<td>0.860</td>
<td>0.740</td>
<td>0.260</td>
</tr>
<tr>
<td>IP30</td>
<td>Symptoms come and go in cycles</td>
<td>CYCLICAL TIME</td>
<td>0.792</td>
<td>0.627</td>
<td>0.373</td>
</tr>
<tr>
<td>IP31</td>
<td>Kidney problem if unpredictable</td>
<td>CYCLICAL TIME</td>
<td>0.770</td>
<td>0.592</td>
<td>0.408</td>
</tr>
<tr>
<td>IP32</td>
<td>Cycles where kidney problem gets better/worse</td>
<td>CYCLICAL TIME</td>
<td>0.834</td>
<td>0.695</td>
<td>0.305</td>
</tr>
<tr>
<td>C1</td>
<td>Stress or worry</td>
<td>PSYCHOLOGICAL CAUSES</td>
<td>0.724</td>
<td>0.524</td>
<td>0.476</td>
</tr>
<tr>
<td>C4</td>
<td>Diet</td>
<td>PSYCHOLOGICAL CAUSES</td>
<td>0.559</td>
<td>0.313</td>
<td>0.687</td>
</tr>
<tr>
<td>C8</td>
<td>Own Behaviour</td>
<td>PSYCHOLOGICAL CAUSES</td>
<td>0.692</td>
<td>0.479</td>
<td>0.521</td>
</tr>
<tr>
<td>C9</td>
<td>Mental Attitude</td>
<td>PSYCHOLOGICAL CAUSES</td>
<td>0.915</td>
<td>0.838</td>
<td>0.162</td>
</tr>
<tr>
<td>C10</td>
<td>Family Problems</td>
<td>PSYCHOLOGICAL CAUSES</td>
<td>0.868</td>
<td>0.754</td>
<td>0.246</td>
</tr>
<tr>
<td>C11</td>
<td>Overwork</td>
<td>PSYCHOLOGICAL CAUSES</td>
<td>0.703</td>
<td>0.494</td>
<td>0.506</td>
</tr>
<tr>
<td>C12</td>
<td>Emotional State</td>
<td>PSYCHOLOGICAL CAUSES</td>
<td>0.901</td>
<td>0.811</td>
<td>0.189</td>
</tr>
<tr>
<td>C13</td>
<td>Ageing</td>
<td>EXTERNAL CAUSES</td>
<td>0.545</td>
<td>0.297</td>
<td>0.703</td>
</tr>
<tr>
<td>C14</td>
<td>Alcohol</td>
<td>EXTERNAL CAUSES</td>
<td>0.819</td>
<td>0.671</td>
<td>0.329</td>
</tr>
<tr>
<td>C15</td>
<td>Smoking</td>
<td>EXTERNAL CAUSES</td>
<td>0.786</td>
<td>0.618</td>
<td>0.382</td>
</tr>
<tr>
<td>C16</td>
<td>Accident or injury</td>
<td>EXTERNAL CAUSES</td>
<td>0.742</td>
<td>0.551</td>
<td>0.449</td>
</tr>
<tr>
<td>C17</td>
<td>Personality</td>
<td>EXTERNAL CAUSES</td>
<td>0.898</td>
<td>0.806</td>
<td>0.194</td>
</tr>
<tr>
<td>C18</td>
<td>Altered Immunity</td>
<td>EXTERNAL CAUSES</td>
<td>0.756</td>
<td>0.571</td>
<td>0.429</td>
</tr>
</tbody>
</table>

*Standardised loading. Items shown are the questions from the IPQ-R. “ID” refers to illness identity items, “IP” to man body of items (consequences, Coherence, Cyclical time-line) and “C” to causal items.*
8.3.7 Structural Equation Model of the Baseline data: the relationship between path to dialysis, illness perceptions and depression

In an initial SEM path to dialysis was specified to predict several illness perceptions which in turn were specified to predict depression (total BDI score, see figure 8.2). A direct path between path to dialysis and depression was also specified. Age, physical function (KPS) and co-morbidity were all entered in the model as interrelated variables, and were all specified to have direct effects upon depression. Physical function was regressed on path to dialysis, and an indirect effect between path to dialysis and depression through physical function.

This model yielded good fit as determined by several fit indices (CFI=0.952, TLI=0.958, RMSEA=0.079), although the chi-square was significant ($X^2 = 157.1$ df=79, $p<0.001$). Path to dialysis predicted illness coherence, cyclical timeline perceptions, and marginally predicted perceived consequences. Specifically unplanned path to dialysis predicted less illness coherence, greater perceptions of cyclical symptoms, and stronger perceptions of psychological causes. Path to dialysis did not have a significant direct effect on depression in the SEM.

In addition, path to dialysis predicted physical performance score (KPS). Lower illness coherence, greater perceived consequences and higher cyclical timeline predicted depression scores. Shown in figure 8.2 are the standardized model estimates. A one standard deviation increase in illness coherence was associated with a -0.23 standard deviation change in depression. A point standard deviation increase in consequence and cyclical timeline perceptions, increases the BDI by 0.36 and 0.21 standard deviations respectively.

Age and KPS had a negative relationship with depression; however co-morbidity was unrelated to depression. Age, KPS and co-morbidity were all inter-correlated (figure 8.2). Age was negatively related with KPS and positively associated with co-morbidity. As expected KPS was negatively correlated with co-morbidity. Age and co-morbidity both correlated negatively with illness identity.

Indirect effects between path to dialysis and depression, through physical performance and the illness perceptions were tested. The overall indirect effect between path to dialysis and
depression was significant (standardized estimate=0.30, p<0.001). Specifically there were indirect effects between path to dialysis and depression through illness coherence (standardized estimate=0.06, p=0.013), and through cyclical perceptions (standardized estimate=0.06, p=0.034). This suggests, albeit from cross-sectional analysis, that illness perception mediate the association between path to dialysis and depression.

Furthermore there was an indirect effect of path to dialysis on depression through KPS (standardized estimate=0.106, p<0.001).

Model trimming was attempted by removing the non-significant paths from the model depicted in figure 8.2. This trimmed model is shown in figure 8.3. A DIFFTEST between the original and the trimmed (i.e. nested model) suggest that the two models did not differ significantly (p=0.07). The trimmed model showed good fit as determined by the fit indices (CFI=0.951, TLI=0.958, RMSEA=0.079). The indirect effects between path to dialysis and depression stated above were maintained in this model. In addition an indirect effect through consequences was tending towards significance (p=0.07).

Alternative SEM models were tested, which included the following variables; treatment control, personal control, timeline and emotion, haemoglobin, albumin and gender. None of these variables were associated with depression, and the model fit did not improve significantly beyond the models described in figures 8.2 and 8.3.
Figure 8.2: SEM between path to dialysis, illness perceptions and depression at baseline (note correlations between the latent variables and error terms have been emitted in this figure but did feature in the modelling).
Figure 8.3: Trimmed SEM between path to dialysis, illness perceptions and depression at baseline (note correlations between the latent variables and error terms have been emitted in this figure but did feature in the modelling).

Shown are standardised estimates

8.4 Results Part II: Analysis of Longitudinal Data

8.4.1 Change in depression symptoms and illness perceptions over time using Linear Latent Growth Models

The observed means with 95% confidence intervals, for BDI and illness perception scores at baseline (n=160), 6 month follow-up (n=133) and 12 month follow-up (n=106) are displayed in table 8.4. In order to establish the trajectory of depression and each illness perception of the IPQ-R, a series of Latent Growth Models were evaluated using Mplus. As described in the methods, each model assumed linear growth.

A summary of the LGMs are presented in table 8.5 including the mean and variance of both the intercept and slope. There was significant variation in BDI scores at baseline, suggesting inter-individual variability. The mean change for depression was -0.43 over the one year follow-up which was non-significant, suggesting that depression symptoms were relatively stable over this period (table 8.5). Furthermore there was no significant variation in the change over time. All of the illness perceptions showed significant variance at the intercept (i.e. at the baseline). Only two illness perceptions changed significantly over time. Illness identity reduced by -0.59 units (p<0.05) over the follow-up suggesting that illness identity was reducing with time. Furthermore there was a significant amount of variance in the change over time, suggesting that there were individual differences in the change. Illness coherence had an increasing trajectory over time (1 point increase over 1 year) suggesting that illness understanding was improving with time. However there was not a significant amount of variance in the change of coherence over time (table 8.5), suggesting the variability of the slopes for individuals did not differ. Personal control did not differ significant over time with regards to mean change, yet there was significant variation in the scores over time, suggesting that the variance was increasing (i.e. individual scores becoming more divergent over time).
Table 8.4: Means and 95% confidence interval for depression scores and illness perceptions at the baseline, 6 month and 12 month follow-up.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Planned</th>
<th>Unplanned</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 month</td>
<td>12 month</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td>12.2 (10.9–13.6)</td>
<td>10.6 (9.3–11.9)</td>
<td>10.6 (9.0–12.3)</td>
</tr>
<tr>
<td>Illness Identity</td>
<td>4.6 (4.2–5.0)</td>
<td>4.4 (3.8–4.9)</td>
<td>3.9 (3.4–4.5)</td>
</tr>
<tr>
<td>Timeline</td>
<td>24.3 (23.7–25.0)</td>
<td>24.5 (23.8–25.2)</td>
<td>25.1 (24.2–25.9)</td>
</tr>
<tr>
<td>Cyclical</td>
<td>10.4 (9.9–10.9)</td>
<td>10.4 (9.8–11.0)</td>
<td>10.2 (9.5–10.9)</td>
</tr>
<tr>
<td>Consequences</td>
<td>21.8 (21.6–22.4)</td>
<td>21.6 (20.8–22.3)</td>
<td>22.0 (21.2–22.8)</td>
</tr>
<tr>
<td>Personal Control</td>
<td>20.3 (19.6–21.0)</td>
<td>19.9 (19.1–20.7)</td>
<td>19.7 (18.9–20.5)</td>
</tr>
<tr>
<td>Treatment Control</td>
<td>16.7 (16.2–17.2)</td>
<td>16.1 (15.6–16.7)</td>
<td>16.3 (15.7–16.9)</td>
</tr>
<tr>
<td>Illness Coherence</td>
<td>17.4 (16.7–18.1)</td>
<td>18.3 (17.5–19.0)</td>
<td>18.6 (17.7–19.5)</td>
</tr>
<tr>
<td>Emotion</td>
<td>17.3 (16.4–18.1)</td>
<td>16.5 (15.7–17.4)</td>
<td>16.4 (15.4–17.5)</td>
</tr>
<tr>
<td>Psychological Causes</td>
<td>14.2 (13.4–15.0)</td>
<td>14.1 (13.4–14.9)</td>
<td>13.8 (12.9–14.8)</td>
</tr>
<tr>
<td>Risk Factor Causes</td>
<td>11.4 (10.7–12.0)</td>
<td>11.7 (11.0–12.4)</td>
<td>11.5 (10.8–12.3)</td>
</tr>
<tr>
<td>External Causes</td>
<td>7.1 (6.8–7.4)</td>
<td>7.2 (6.8–7.6)</td>
<td>7.1 (6.6–7.6)</td>
</tr>
</tbody>
</table>
Table 8.5: Summary of a series of linear Latent Growth Models for depression scores and illness perceptions over a one year follow-up.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean of Intercept</th>
<th>Variance of Intercept</th>
<th>Mean of change</th>
<th>Variance of change</th>
<th>Covariance between level and change</th>
<th>Model $\chi^2$ (df)</th>
<th>CFI</th>
<th>RMSEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>11.6 (0.7)**</td>
<td>44.6 (8.8)**</td>
<td>-0.43 (0.7)</td>
<td>15.4 (18.4)</td>
<td>-1.4 (10.1)</td>
<td>6.5 (1)</td>
<td>0.971</td>
<td>0.187</td>
</tr>
<tr>
<td>Identity</td>
<td>4.6 (0.2)**</td>
<td>6.4 (1.3)**</td>
<td>-0.59 (0.7)*</td>
<td>5.1 (2.4)*</td>
<td>-2.7 (1.4)</td>
<td>0.0 (1)</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Timeline</td>
<td>24.3 (0.3)**</td>
<td>11.5 (3.0)**</td>
<td>0.47 (0.4)</td>
<td>6.9 (6.2)</td>
<td>-3.1 (3.9)</td>
<td>0.8 (1)</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Consequences</td>
<td>21.7 (0.3)**</td>
<td>11.3 (2.5)**</td>
<td>0.28 (0.3)</td>
<td>3.8 (4.5)</td>
<td>-2.4 (2.7)</td>
<td>1.9 (1)</td>
<td>0.992</td>
<td>0.07</td>
</tr>
<tr>
<td>Personal Control</td>
<td>20.3 (0.3)**</td>
<td>17.9 (3.2)**</td>
<td>-0.58 (0.4)</td>
<td>16.8 (5.3)**</td>
<td>-10.4 (3.5)**</td>
<td>0.0 (1)</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Treatment control</td>
<td>16.6 (0.2)**</td>
<td>5.7 (1.6)**</td>
<td>-0.5 (0.3)</td>
<td>2.8 (3.2)</td>
<td>-1.7 (1.8)</td>
<td>3.1 (1)</td>
<td>0.97</td>
<td>0.115</td>
</tr>
<tr>
<td>Cyclical timeline</td>
<td>10.4 (0.3)**</td>
<td>5.4 (1.8)**</td>
<td>0.03 (0.3)</td>
<td>-0.3 (3.9)</td>
<td>1.5 (2.2)</td>
<td>0.2 (1)</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Coherence</td>
<td>17.5 (0.3)**</td>
<td>10.2 (2.9)**</td>
<td>1.0 (0.3)**</td>
<td>-7.7 (6.1)</td>
<td>3.9 (3.5)</td>
<td>0.8 (1)</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Emotion</td>
<td>17.1 (0.4)**</td>
<td>15.0 (3.7)**</td>
<td>-0.4 (0.4)</td>
<td>-5.9 (7.6)</td>
<td>5.6 (4.2)</td>
<td>1.3 (1)</td>
<td>0.998</td>
<td>0.045</td>
</tr>
<tr>
<td>Psychology Causes</td>
<td>14.2 (0.4)**</td>
<td>12.4 (3.3)**</td>
<td>-0.4 (0.4)</td>
<td>-6.5 (6.9)</td>
<td>3.4 (3.9)</td>
<td>0.02 (1)</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>External Causes</td>
<td>7.1 (0.2)**</td>
<td>2.7 (0.7)**</td>
<td>0.2 (0.2)</td>
<td>2.3 (1.6)</td>
<td>-0.3 (0.9)</td>
<td>0.3 (1)</td>
<td>1.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*a* unstandardised estimates *p*<0.05 **p*<0.01
8.4.2 Unspecified latent growth model for depression

As described above, depression did not change significantly over the year follow-up as evaluated by a linear latent growth model. However examination of the observed means as shown in figure 8.4 suggests that there is an initial decline in depression symptoms from baseline to 6 month follow-up which then stabilises from 6 months to 12 months.

**Figure 8.4:** Observed and estimated means for the BDI at baseline, 6 and 12 month follow-up.

Furthermore, examination of individual curves taken at random (n=10) suggests a pattern of declining BDI scores from baseline- 6 month follow-up (figure 8.5). Further, inspection of figure 8.5 suggests that there may well be different clusters of trajectories (those who stay constant, those who decline over time and those improve over time). However to test this in “latent class” analysis would require a very large sample size thus was not attempted here. Nevertheless, it appears that any potential change in depression scores may be non-linear. Conventionally this could be tested by entering a quadratic term into the growth model; however for the model to be identified there needs to be a minimum of 4 time points. Given this, an unspecified latent growth model for depression was examined where the final time slope was freed to be estimated (see methods). This essentially allows the growth to be estimated, rather than stipulating that the growth is linear. An unspecified latent growth model as depicted in figure 8.6 was examined in Mplus. The model was
saturated (i.e. just identified) as there were no degrees of freedom following model estimation. As expected from a saturated model the model provided excellent fit according to the fit indices (CFI=1, TLI=1 and RMSEA=0.0). As shown in figure 8.6 the mean at the intercept was 12.2 (SE=0.7).

Figure 8.5: A random selection of 10 individual growth curves for BDI scores over time.

Further, there was significant variation at the intercept. The mean change as estimated by the model was -2.8 (p=0.013) suggesting that depression scores decreased over time. There was no significant variation in the change over time (p=0.521). Furthermore the intercept and slope did not share a significant amount of co-variation (p=0.99). This suggests that depression may be declining over time during the first year of dialysis (probably the first 6 months), although the change appears to be non-linear. However it should be noted that there are not enough time points to evaluate the function of the change over time and that there is not a significant amount of variance in the change over time. Taken together there appears to be a trend for declining depression scores over the first 6 months of dialysis.
8.4.3 Predictors of the change in depression

Predictors of the change in depression were evaluated by regressing the intercept and slope from the linear growth model described above onto the following independent variables, age, kps, path to dialysis, co-morbidity, and the illness perceptions. In other words do particular independent variables predict the intercept (i.e. the initial starting values at baseline) and the change in depression scores over a year follow-up? The linear growth model, and not the unspecified latent growth model, for depression was chosen here because the interpretation of non-linear change with only three time points is difficult, particularly when regressing upon an independent variable. Initially each independent predictor was entered separately into a latent growth model in order to retain power. Table 8.6 displays a summary of the slope and intercepts which were regressed upon the independent variable. Several independents variables predicted the intercept (i.e. the baseline BDI score) which have been described in detail in the SEM reported above.

With regards to potential factors that predict the change (slope) in depression neither age, kps, co-morbidity or path to dialysis were associated with the trajectory of depression over time (table 8.6). In addition the effect of baseline Haemoglobin, Albumin and treatment
modality on the change in depression scores was tested in subsequent models, and revealed non-significant findings.

Several of the baseline IPQ-R perceptions predicted the trajectory of depression, namely time-line perceptions, illness coherence, external causes and emotion (table 8.6). A one point increase in timeline perception at baseline was associated with a 0.63 unit increase in BDI scores over time. A one point increase in illness coherence at baseline is expected to predict a 0.33 increase in BDI score over-time. External causes also predicted the trajectory of depression, with a one point baseline increase being associated with a -0.602 unit decrease in BDI scores over time. As expected, emotion representations predicted the change in depression over time, with a one point increase at baseline being associated with a -0.38 decrease in BDI scores. These four illness perceptions were entered into a multivariate latent growth model where the depression intercept and slope was regressed upon them. This model is shown in figure 8.7 and had good fit to that according to the fit indices (CFI=0.978, TLI=0.935, RMSEA=0.091). After controlling for coherence and external cause perceptions, both timeline and emotion predicted the trajectory of depression in this multivariate model (figure 8.7). A one point increase in timeline perception at baseline was associated with a 0.56 unit increase in BDI scores over time. Emotion representations predicted the change in depression over time, with a one point increase at baseline being associated with a -0.27 decrease in BDI scores.

Adding other variables to the model described in figure 8.7 including, age, path to dialysis, KPS did not improve the model fit significantly, nor did any of the variables predict the trajectory of depression.
Table 8.6: Predictors of the intercept and slope in a linear latent growth model of depression.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate on intercept&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Estimate on slope&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CFI</th>
<th>RMSEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.111**</td>
<td>0.027</td>
<td>0.972</td>
<td>0.133</td>
</tr>
<tr>
<td>Gender</td>
<td>2.55</td>
<td>-0.73</td>
<td>0.976</td>
<td>0.122</td>
</tr>
<tr>
<td>KPS</td>
<td>-0.237**</td>
<td>0.056</td>
<td>0.968</td>
<td>0.148</td>
</tr>
<tr>
<td>Path</td>
<td>4.75**</td>
<td>-1.196</td>
<td>0.978</td>
<td>0.118</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>0.747</td>
<td>0.034</td>
<td>0.960</td>
<td>0.156</td>
</tr>
<tr>
<td>Identity</td>
<td>1.03**</td>
<td>-0.018</td>
<td>0.963</td>
<td>0.160</td>
</tr>
<tr>
<td>Timeline</td>
<td>-0.176</td>
<td>0.626**</td>
<td>0.979</td>
<td>0.115</td>
</tr>
<tr>
<td>Consequences</td>
<td>0.837**</td>
<td>-0.03</td>
<td>0.976</td>
<td>0.131</td>
</tr>
<tr>
<td>Personal Control</td>
<td>-0.149</td>
<td>-0.104</td>
<td>0.965</td>
<td>0.147</td>
</tr>
<tr>
<td>Treatment control</td>
<td>-0.270</td>
<td>-0.277</td>
<td>0.973</td>
<td>0.130</td>
</tr>
<tr>
<td>Cyclical timeline</td>
<td>0.680**</td>
<td>-0.320</td>
<td>0.971</td>
<td>0.136</td>
</tr>
<tr>
<td>Coherence</td>
<td>-0.570**</td>
<td>0.322*</td>
<td>0.972</td>
<td>0.137</td>
</tr>
<tr>
<td>Emotion</td>
<td>1.047**</td>
<td>-0.388**</td>
<td>0.977</td>
<td>0.144</td>
</tr>
<tr>
<td>Psychology Causes</td>
<td>0.313*</td>
<td>-0.191</td>
<td>0.976</td>
<td>0.121</td>
</tr>
<tr>
<td>External Causes</td>
<td>0.805**</td>
<td>-0.602*</td>
<td>0.976</td>
<td>0.122</td>
</tr>
</tbody>
</table>

<sup>a</sup>Unstandardised p<0.05**p<0.01
Figure 8.7: Illness perceptions predicting the intercept and slope of depression over a year follow-up (note correlations between the observed independent variables and errors for the dependent variables are emitted from the figure).

8.5 Discussion

The study presented here is the first to examine the trajectory of depression over the first year of dialysis in relation to illness perceptions. Corroborating with data from the preceding chapter, the present analysis supports the thesis that illness perceptions and depression are related. Moreover the data here has shown that illness perceptions predict the trajectory in depression over time. The discussion will focus on three key aspects of the findings, 1) the baseline associations between path to dialysis, illness perception and depression, 2) the change in depression and illness perceptions over time, and 3) illness perceptions predicting the trajectory of depression over time.

The data provides support for the first hypothesis tested here, that unplanned patients hold different illness perceptions at baseline as compared to planned patients. Indeed the findings here are novel and demonstrate that unplanned patients had lower time-line perceptions, greater perceptions of disease variability (cyclical-time-line), adverse
consequences and emotional response, and lower illness coherence as compared with patients who had planned starts. With regards to the causal items, unplanned starters had stronger perceptions of external and psychological causes compared to planned patients. Furthermore a similar pattern of differences with regards to illness perceptions were observed between the depressed and non-depressed patients at baseline supporting the differences observed in the cross-sectional study of chapter 7. In addition, univariate analysis revealed that unplanned patients scored significantly higher on the BDI, as compared to planned patients thus supporting the data of Miura et al (1999).

In SEM path to dialysis predicted several illness perceptions. Furthermore illness perceptions predicted depression symptoms. In line with the cross-sectional data presented in chapter 7 greater cyclical perceptions and perceived consequences and lower illness coherence predicted depression scores. Again the finding that illness perceptions are associated with depression symptoms supports previously published data reviewed in chapter 3 (Jopson & Moss-Morris, 2003; Juergens et al., 2010; Murphy et al., 1999). This is of interest as in chapter 7 depression was treated as a categorical dependent variable, whereas in the current analysis depression was treated as a continuous dependent variable, yet similar findings were uncovered using both approaches. Moreover as found in chapter 7, clinical variables including co-morbidity did little to explain the variation in depression scores, rather it was the interpretation of the condition that contributed to its explanation (e.g. Sacks et al., 1990).

Interestingly there was no direct association between path to dialysis and depression after controlling for illness perceptions, yet there was evidence of an indirect effect (i.e. mediation) between path to dialysis and depression through perceptions. This data suggests that starting dialysis in an unplanned manner led to a different interpretation of the illness threat, which in turn increased the vulnerability for depression. It is important to note however, that this association is derived from the baseline data (hence cross-sectional associations) thus caution is merited in its interpretation as it is possible that path to dialysis increased depression symptoms which in turn impacted upon illness perception via negative depressive schema.
Consistent with findings from elsewhere in literature concerning depression in physical illnesses, in the present study, age and physical performance were negatively associated with depression scores (Drayer et al., 2006; Egede, 2007; Lopes et al., 2002). Younger age and worse physical performance were predictive of depression in the SEM after controlling for co-morbidity and illness perceptions. Treatment modality was unrelated to depression in the analysis reported here, although there is mixed evidence regarding differences between dialysis modalities and depression (Brown et al., 2010; Martin, Tweed, & Metcalfe, 2004; Zimmermann, Poli de Figueiredo, & Fonseca, 2001). These findings may relate to lack of power as differences between dialysis modalities were not the focus of this study.

With regards to examining changes over time, there are few data in ESRD describing the course of depression. Furthermore, there are relatively few studies that have examined the dynamics of illness perceptions among chronic physical conditions (Fischer et al., 2010). Using LGMs, the data here suggests that depression was relatively stable over time, thus there was no reliable evidence for the hypothesis that depression declines over the first year of treatment. A caveat is that with only three time points the function of change is hard to define. There was some suggestion in the unspecified LGM that depression scores were in fact decreasing over time suggesting a potentially non-linear decline. Further examining individual trajectories (e.g. figure 8.5) suggest that some patients may be stable, whilst some improve and others worsen over time. Unfortunately the sample size inhibited the undertaking of latent class growth analysis which is an appropriate technique to examine clusters of trajectories over time, and their predictors. While there appeared to be a significant amount of variation in the BDI scores at the baseline data, the variance in the change over time was non-significant, which again suggests relative stability in the inter-individual change over time (i.e. variability of the slope). To note, the variance of the slope was large suggesting that some variability was occurring between patients yet it is possible that the limited follow-up period and sample size influenced the significance test here.

Others suggest that depression may be stable in dialysis patients (Cukor et al., 2008), while data in incident patients suggest that there may be improvements in mental health functioning during the first year of dialysis therapy (Korevaar et al., 2002). Moreover studies that have compared CKD and ESRD patients suggest that the level of depression is comparable between populations (Abdel-Kader, Unruh, & Weisbord, 2009; Hedayati et al.,
Although anecdotal this may suggest that depression is prevalent in CKD and remains so through to dialysis (ESRD).

With regards to the trajectories of illness perceptions over time, past data among chronic illness groups suggest that timeline and coherence perceptions increase over time, while control perceptions and emotional reaction decrease (Bijsterbosch et al., 2009; Lawson et al., 2008; Sheldrick et al., 2006). Covic et al (2006) report that over a two year follow-up of dialysis patients, emotional reactions decreased while coherence and treatment control perceptions improved. The data here revealed a similar trajectory for illness coherence, that is over the one year follow-up, patients’ understanding significantly increased. In addition, illness identity decreased significantly suggesting that individuals tended to identify their ESRD with fewer somatic symptoms over time. Contrary to previous published data there was no evidence here of increasing timeline perceptions over time, nor decreasing control perceptions and emotional reactions. It is possible that timeline and control perception did not change because the study focused on incident dialysis patients, whereas Covic et al assessed established patients over a longer period.

Establishing the predictors of change in depression was sought by regressing the slope of LGMs upon independent variables. Firstly no baseline demographic or clinical variables including path to dialysis predicted the change in depression over time. This is particularly interesting as it suggests albeit tentatively that the differences between planned and unplanned patients depression scores at baseline is maintained over the first year of therapy. Of course more advanced modeling is required in order to test this assumption, however the sample size and follow-up period presented here prohibits such analysis. Nevertheless the data from the LGMs revealed that path to dialysis does not predict change over time.

The final hypothesis stated in this chapter was that illness perceptions would predict the trajectory of depression over time. In growth models where each illness perception was entered separately, several baseline perceptions predicted the change in depression over time. Examination of the predictors in multivariate model revealed that baseline timeline perceptions and emotion reactions predicted the change in depression over time. Higher chronicity perceptions at baseline predicted an increase in depression, while a greater
emotional reaction at baseline predicted a decline in depression. With regards to timeline perceptions, Dickens et al (2008) demonstrated that such perceptions predicted later depression in MI patients. Greater baseline emotion predicting a decrease in depression over time may suggest that patients are self-regulating their initial distress at baseline and focusing efforts to improve mood. This may explain why emotion correlates negatively with BDI change over time. Increasing control perceptions did not feature as predictors of depression change. Others report that control perceptions predict later levels of depression, which conforms to psychological theories with regard to hopelessness as antecedents for depression (Abramson, Alloy, & Metalsky, 1989). The stability of control perceptions over time may be the result of unpowered LGMs, or because during a relatively short term follow-up such perception are unlikely to vary, particularly as most patients were receiving in-hospital HD. What was of interest is that the variability in personal control scores did vary over time, suggesting that there was more divergence as time went by, which may be detrimental to psychological outcomes at points later on in the dialysis career.

Taken together this data shows that depression and illness perception share a strong cross-sectional association and that unplanned dialysis initiation is associated with maladaptive illness perceptions which may predispose an individual to depression. Furthermore the majority of illness perceptions appear somewhat stable during the first year of therapy presumably as little ongoing education and support is given to patients, although the variances of the change were large suggesting some between patient variance in trajectories. Path to dialysis failed to predict a change in depression, and although not reported in the results, failed to predict change in any of the illness perceptions variables. Rather, the data here suggests that initial illness perceptions can predict the trajectory of depression over this period, although the amount of change overtime at a group level is small, and individual trajectories do vary. Preliminary evidence here suggests that patients may well be self-regulating mood over a year or so of therapy, yet there clearly is a requirement to target maladaptive illness perceptions via psychological intervention soon after patients start dialysis. In this regard tacking the maladaptive perceptions of unplanned dialysis starters seems particularly vital.
While the data here has provided evidence in support of the thesis, it is worthy to consider the study limitations. It is clear that in order to further define the trajectory of depression larger studies with longer follow-up are required. Extending the study would also allow dual growths to be examined, where the change (slope) of a perception could be specified to predict the change (slope) of depression. This would further add to the data here and allow extended hypothesis to be evaluated. Furthermore, it is clear than depression is a multifaceted psychopathology and that several factors not considered here may help further explain variation in the depression among individual with ESRD, including social support, deprivation and marital satisfaction. A further limitation relates to the absence of time since diagnosis data. While data on depressive history was collected from the medical notes, it is probable that this method is somewhat crude as unplanned patients may not have such a detailed history document at the beginning of dialysis. Given this significant limitation data on depression history was not included in the modelling yet it is acknowledge that a history of depression is a known predictor of depression in renal patients (Cukor et al., 2008).

8.5 General comments

As evident in the last two chapters illness perceptions share a close relationship with depression. Coherence, cyclical timeline and perceived consequences appear to be particularly important perceptions in this regard. Moreover the data here shows that timeline perceptions and emotional reactions predict the trajectory of depression over the first year of treatment, although by-and-large both depression and illness perceptions appear relatively stable over this period.

The following chapter develops the argument that illness representations posited by the CSM have utility beyond the explanation of depression in ESRD. Specifically chapter 9 investigates whether there is an association between illness perceptions and fluid non-adherence in a sample of haemodialysis patients. Non-adherent behaviour is of particular interest as it is associated with adverse clinical outcomes in dialysis patients, thus attempting to understand apparent self-regulatory failure is important.
Chapter 9

An Illness Representation approach to the understanding of Fluid Non-adherence 12

9. 1 Introduction

The preceding empirical chapters inform the cardinal features of this thesis, describing the associations between depression and illness representations. The aims of this section are to extend the scope of the work presented thus far with respect to its clinical application. In the chapters to follow two clinical areas are addressed; 1) the utility of the Common Sense Model of illness representations for explaining specific ESRD health behaviour, and 2) the impact of depression and illness perceptions upon survival among incident dialysis patients.

First the CSM and adherence is considered in the present chapter. As delineated in chapter 3, the utility of exploring illness representations in relation to health-related outcomes, including health behaviour, functional outcome and psychological adaptation, has received support from several sources. Unlike other models of health behaviour (e.g. health belief model) the CSM posits a dynamic process in which health related decisions (or coping procedures) are taken in response to a health threat. Further, in the context of adherence, a treatment or behavioural requirement (e.g. fluid restriction) is viewed as a potential facet of coping, whereby its uptake is dependent upon the interpretation of the current illness threat. More recently Robert Horne has developed the necessity-concerns framework, which addresses the cognitions surrounding medication adherence (Horne, 1997; Horne & Weinman, 1999). While the necessity-concerns framework is a useful extension to the CSM, it has not been operationalised to other protective health behaviours (e.g. fluid restriction).

For a given health behaviour the CSM stresses the importance of coherence between the illness representation and coping procedure. Accordingly, the process of self-regulation is operationalised through “IF-THEN” rules (Leventhal et al., 1998, see chapter 3).

12To note, a paper based on this chapter has been published in Chilcot, J., Wellsted, D., Farrington, K (2010). Illness perceptions are associated with fluid non-adherence among haemodialysis patients. Journal of Psychosomatic Research, 68 (2), 203-212.
9.1.1 Adherence on dialysis

Dialysis is a time consuming and stressful activity. The complications of ESRD require numerous additional treatments including multiple drugs to facilitate management of blood pressure, anaemia, abnormalities of mineral metabolism, and other problems related to extra-renal co-morbidities. A potential stressor is the need to restrict dietary intake of phosphates and potassium rich foods, and reduce salt and fluid intake. Adherence to ESRD can therefore be categorised into the following facets; 1) medication, 2) dietary and fluid, and 3) dialysis prescription (Lamping & Campbell, 1990). Indeed, the adaption and maintenance to these requirements are crucial in the disease management.

Fluid non-adherence is one particular concern that is regularly observed in clinical practice. It is associated with adverse clinical outcomes including left ventricular hypertrophy, cardiac failure and premature death (Leggat et al., 1998). Fluid intake is driven by thirst which is strongly related to the body's sodium balance. Estimates of fluid non-adherence are varied and largely dependent upon methodology and definition. Typically, fluid intake is evaluated by inter-dialytic weight gain (IDWG). IDWG refers to the amount of fluid gained between two dialysis treatment sessions, and is estimated by subtracting the post-dialysis weight from the pre-dialysis weight of the following treatment session. Although IDWG serves as a suitable physiological proxy of fluid adherence (Manley & Sweeney, 1986), the heterogeneity of definitions used has had a major impact upon reported estimates of non-adherence. Critically IDWG alone is insufficient to define non-adherence, as it is influenced by residual renal function (the amount of intrinsic renal function the patient has remaining) (Manley & Sweeney, 1986), and dry weight (the patients “ideal weight” when free of excess fluid) (Chazot et al., 1999; Sensky, Leger, & Gilmour, 1996). The failure to consider these parameters when assessing fluid non-adherence based upon IDWG may lead to inaccurate prevalence rates and misidentified antecedent factors. The present empirical work addressed both of these issues.

9.1.2 Predictors of non-adherence in ESRD

Several factors have been associated with non-adherence among dialysis patients including age, gender, and psychological factors such as health beliefs (Cummings, Becker, Kirscht, & Levin, 1982; Kutner, Zhang, McClellan, & Cole, 2002), social support (Kara, Caglar, & Kilic,
2007; O'Brien, 1990), personality factors (Christensen & Smith, 1995), locus of control and self-efficacy (Brady, Tucker, Alfino, Tarrant, & Finlayson, 1997; Kutner et al., 2002; Sensky et al., 1996), and depression (Cukor et al., 2009). Evidence tends to support the increased predictive utility of cognitive factors over emotional states (Schneider, Friend, Whitaker, & Wadhwa, 1991). However it is likely that these factors have complex interactions and vary with different behavioural demands (Sensky et al., 1996). The application of social-cognitive models of health behaviour in ESRD patients has received surprisingly little attention, yet promises utility given empirical work in other health domains. Currently only one study has demonstrated the predictive utility of the CSM model in explaining self-care behaviour in HD patients, although when applied specifically to fluid intake behaviour, illness representations (both cognitive and emotional) failed to explain the variation in IDWG (O'Connor et al., 2008).

9.1.3 The present Study

This study investigated whether there were significant differences between fluid-adherent and non-adherent patient’s illness representations, as measured by the IPQ-R. In addition, whether illness representations predicted fluid non-adherence was tested. The definition of fluid non-adherence involved computing IDWG as a percentage of patient’s dry weight, thus reducing potential confound. Although investigating the variation of IDWG in relation to hypothesised predictive factors is of value, it was felt that exploring the psychology of a clinically relevant patient group, who would be at greater risk of developing fluid-related complications, would be more clinically useful. In order to achieve this goal, patients in the upper-quartile of the percentage weight gain distribution were defined as non-adherence and subsequently compared to the remaining patient sample.

Given these methodological considerations, it was hypothesized that, 1) in univariate analysis, there would be significant differences between illness perceptions of adherent versus non-adherent patients, and 2) illness perceptions would be associated with fluid adherence after controlling for clinical and demographic factors including residual renal function, thus supporting the utility of the CSM in this context.
9.2 Methods

9.2.1 Patients

A sample of adult HD patients from the renal service of the East and North Hertfordshire NHS Trust were approached for inclusion, provided they satisfied the criteria described in chapter 4 (general methods). All patients were required to be receiving HD 3 times per week.

9.2.2 Materials

*Demographic questionnaire:* Age, gender, ethnicity, marital-status, and work-status were collected by means of a questionnaire (see general methods chapter 4).

*The Revised Illness Perception Questionnaire (IPQ-R):* As described in chapter 4. *To note,* The sample size prevented factor analysis on the 18 original IPQ-R causal items. The mean scores on each individual causal item were compared between the adherence groups.

*Depression Symptoms:* Depression symptoms were assessed via the Beck Depression Inventory (BDI-II) as described in Chapter 4.

*Functional Status and Comorbidity:* Karnofsky Performance Score was employed to assess functional status. Comorbidity was assessed using a semi-quantitative technique, scored by consultant nephrologist who assigned a severity score for each patient (1= no co-morbidity, 2= mild moderate co-morbidity, 3= severe co-morbidity, as described in Chandna et al., 1999, see chapter 4).

*Clinical parameters:* Standard haematological and biochemical parameters are collected as a part of the routine care of patients within the service. These include blood levels of haemoglobin, albumin, and urea. Dialysis adequacy (Kt/V), dry weight (kg), and residual renal function (measured by urea clearance (KRU, ml/min)) were also assessed. KRU is measured routinely in this dialysis centre, and included in urea kinetic modelling, as recommended in the national kidney foundation guidelines for HD adequacy (KDOQI, 2006). KRU was derived from a 48 hour interdialytic urine collection, and mean interdialytic urea concentration\textsuperscript{13} (McKane, Chandna, Tattersall, Greenwood, & Farrington, 2002). Dry

\textsuperscript{13} the mean of the pre- and post-dialytic serum urea concentrations
weight (or “ideal weight”) is the principle target for fluid removal in dialysis, and refers to the normal fluid weight of the patient (euvolemic), without oedema or excess interstitial fluid. IDWG was computed by subtracting the post-dialysis weight from the pre-dialysis weight of the following treatment session (kg). All clinical parameters were averaged over a three month period prior to the administration of the IPQ-R. This included the clinical parameters obtained during the month of the IPQ-R assessment. KRU was measured every month, IDWG every dialysis session (3 times per week), with all other clinical parameters collected at least monthly as part of routine practice. Clinical variables were averaged due to the potential error in single clinical parameter estimates.

Measuring fluid intake and defining adherence: The definition of adherence was based upon IDWG and dry weight (Leggat et al., 1998). IDWG is insufficient to estimate adherence; a larger person is expected to gain more weight in the interdialytic period. However IDWG is a good indicator of fluid intake as long as KRU and dry weight are taken into account. IDWG was therefore computed as a percentage of the patient’s dry weight (i.e. percentage weight gain). In-order to define a group of patients that represent a clinical concern given inadequate fluid control, patients in the upper quartile of the % weight gain distribution (non-adherent) were compared to those in the lower three quartiles (adherent). The upper quartile (i.e. non-adherent patients) had IDWGs ≥3.21% of dry weight. In other words, over the interdialytic period the non-adherent patients were defined as those who had increased their body weight by at least 3.21% of their clinically ideal weight. The mean % weight increase in the non-adherent group was 4.0% (sd= 0.9), compared to 1.9% (sd=0.7) in the adherent group.

9.2.3 Design and Procedure:
A cross-sectional design was used in this investigation. Patients who satisfied the inclusion criteria were identified by a nephrologist. Patients completed the questionnaire measures (BDI and IPQ-R) during a stable haemodialysis session, during the second half hour of treatment (see chapter 5). KRU and IDWG data were verified by a consultant nephrologist.
9.3 Results

One hundred and eighteen patients were approached in which one hundred patients provided consent (17 refused, 1 excluded after the administration of the MMSE). One patient was excluded as they had been receiving dialysis only twice a week during the past 3 months. Data on 99 patients is presented, of which the demographic and clinical characteristics are shown in table 9.1. The mean IDWG was 1.77 kg (sd =0.85). Patients weight increased on average by 2.46% (sd =1.2) over the interdialytic period.

Demographic and clinical characteristics between fluid adherent and non-adherent patients are presented in table 9.1. There was a significant association between gender and fluid adherence. Females had greater odds of non-adherence (unadjusted OR=0.34 95% CI 0.13 and 0.87). Non-adherent patients were significantly younger, had higher Kt/V, greater serum urea, lower KRU and more years on dialysis (dialysis vintage) as compared with the adherent patients (table 9.1). There was no significant association between ESRD diagnosis and adherence (Fisher’s exact test, p=0.10).

9.3.1 Illness Representations

Mean scores for each of the IPQ-R dimensions for adherent and non-adherent patients are displayed in table 9.2. On average, patients held strong perceptions of the chronicity and negative consequences of ESRD and moderately strong perceptions of personal and treatment control. Univariate comparisons between adherent and non-adherent patients revealed that time-line perceptions were significantly lower in the non-adherent patients, suggesting that they held weaker perceptions of the chronicity of ESRD (t[30.6]=2.6, p=0.014). Consequences perceptions were higher in the adherent patients as compared to the non-adherent (figure 9.1). Although this different was not significant, a medium univariate effect size was evident (d=0.37).

A MANOVA was also evaluated comparing the illness perceptions between adherent and non-adherent groups (see table 9.2). MANOVA with all the IPQ-R dimensions as dependent variables revealed a marginal non-significant overall effect (F[8,90]=1.9, p=0.057 η²=0.115). As with the univariate analysis time-line was the only perception to differ between the groups in the MANOVA (F[1, 97]=10.5, p=0.002 η²=0.098).
The most frequently endorsed IPQ-R causal item was chance/bad luck attributes (44.4%), followed by hereditary beliefs (30.3%) and poor past medical care (20.2%). Examination of the individual IPQ-R causal item means, revealed no significant differences between the adherence groups.

9.3.2 Clinical and demographic correlates: Age, urea, KRU and dialysis vintage all correlated significantly with % weight gain (table 9.3). As expected, % weight gain correlated significantly with Kt/V and treatment time.

9.3.3 Psychological Correlates: % weight gain correlated significantly with illness identity, time-line and cyclical time-line perceptions (table 9.4). Personal control and treatment control perceptions failed to correlate with % weight gain. Illness identity correlated with the BDI, perceived consequences, cyclical perceptions and emotion. Time-line correlated with the BDI, consequences, personal control, treatment control and emotion scales. Cyclical perceptions correlated with perceived consequences. The only individual causal items to correlate significantly with % weight gain were germ/virus attributes, and emotional attributes.
Table 9.1: Demographic and clinical data: comparing fluid adherent and non-adherent patients.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=99)</th>
<th>Adherent (n=25)</th>
<th>Non-adherent (n=74)</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female % (n)</td>
<td>33.3 (33)</td>
<td>27 (7)</td>
<td>52 (38)</td>
<td>0.028a</td>
</tr>
<tr>
<td>Male % (n)</td>
<td>66.7 (66)</td>
<td>73 (18)</td>
<td>48 (36)</td>
<td></td>
</tr>
<tr>
<td>Age (Mean SD)</td>
<td>58.6 (15.6)</td>
<td>61.1 (14.7)</td>
<td>51.3 (16.1)</td>
<td>t(97)=2.78, p=0.006</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>88.9 (88)</td>
<td>90.5 (23)</td>
<td>84 (62)</td>
<td>0.462a</td>
</tr>
<tr>
<td>Non-White</td>
<td>11.1 (11)</td>
<td>9.5 (2)</td>
<td>16 (12)</td>
<td></td>
</tr>
<tr>
<td>Marital status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living with partner</td>
<td>67.7 (67)</td>
<td>70.3 (18)</td>
<td>60 (44)</td>
<td>X² (2,99)=1.12, p=0.571</td>
</tr>
<tr>
<td>Divorced/separated/single</td>
<td>24.2 (24)</td>
<td>23 (6)</td>
<td>28 (21)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>8.1 (8)</td>
<td>6.8 (1)</td>
<td>12 (9)</td>
<td></td>
</tr>
<tr>
<td>KPS (Median and IQR)</td>
<td>80 (20)</td>
<td>80 (20)</td>
<td>80 (20)</td>
<td>U=911, p=0.907</td>
</tr>
<tr>
<td>Clinical Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic (%)</td>
<td>15.2 (15)</td>
<td>13.5 (3)</td>
<td>20 (15)</td>
<td>0.520a</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>11.1 (11)</td>
<td>9.5 (2)</td>
<td>20 (15)</td>
<td>0.139a</td>
</tr>
<tr>
<td>Co-morbidity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>38.4 (38)</td>
<td>32.4 (8)</td>
<td>56 (41)</td>
<td>X² (2,99)=4.5, p=0.104</td>
</tr>
<tr>
<td>Moderate</td>
<td>41.4 (41)</td>
<td>44.6 (11)</td>
<td>32 (24)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>20.2 (20)</td>
<td>23 (6)</td>
<td>12 (9)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment time (T_d minutes)</td>
<td>191.8 (45.5)</td>
<td>188.8 (48.6)</td>
<td>200.9 (33.7)</td>
<td>t(97)=1.15, p=0.252</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.3 (0.2)</td>
<td>1.2 (0.2)</td>
<td>1.3 (0.2)</td>
<td>t(97)=3.1, p=0.003</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>11.7 (1.4)</td>
<td>11.7 (1.2)</td>
<td>11.6 (1.9)</td>
<td>t(97)=0.42, p=0.672</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>37.9 (3.8)</td>
<td>38 (4.0)</td>
<td>37.8 (3.2)</td>
<td>t(97)=0.23, p=0.814</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>22.6 (5.5)</td>
<td>21.9 (4.9)</td>
<td>24.7 (6.6)</td>
<td>t(97)=2.3, p=0.02</td>
</tr>
<tr>
<td>Dry Weight (Kg)</td>
<td>73.2 (17.9)</td>
<td>74.8 (18)</td>
<td>68.4 (17.2)</td>
<td>t(97)=1.56, p=0.12</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRU (ml/min/1.73m² BSA)</td>
<td>0.4 (1.6)</td>
<td>1.0 (2.0)</td>
<td>0.1 (0.3)</td>
<td>U=502, p=0.001</td>
</tr>
<tr>
<td>Dialysis Vintage (years)</td>
<td>2.6 (4.2)</td>
<td>2.1 (3.2)</td>
<td>3.9 (4.4)</td>
<td>U=596, p=0.001</td>
</tr>
</tbody>
</table>

* p<0.05  ** p<0.01. IQR: Inter-quartile range, SD: standard deviation, aFisher’s Exact Test, t: Student’s t-test, U: Mann-Whitney U, X²: Pearson Chi-square, MMSE: Mini Mental State Examination, KPS: Karnofsky Performance Score, IDWG: Interdialytic weight gain, KRU: Residual Renal Function.
Table 9.2: Mean illness perception scores, comparing the adherent and non-adherent patients using MANOVA.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Adherent</th>
<th>Non-adherent</th>
<th>F</th>
<th>η²</th>
<th>Univariate effect size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>Possible Range</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Identity</td>
<td>0.84</td>
<td>0-14</td>
<td>5.3</td>
<td>3.1</td>
<td>5.1</td>
</tr>
<tr>
<td>Time-line</td>
<td>0.84</td>
<td>6-30</td>
<td>25.9</td>
<td>4.4</td>
<td>26.7</td>
</tr>
<tr>
<td>Cyclical time-line</td>
<td>0.83</td>
<td>4-20</td>
<td>9.7</td>
<td>3.4</td>
<td>9.6</td>
</tr>
<tr>
<td>Consequence</td>
<td>0.69</td>
<td>6-30</td>
<td>21.8</td>
<td>4.2</td>
<td>22.2</td>
</tr>
<tr>
<td>Treatment Control</td>
<td>0.44</td>
<td>5-25</td>
<td>14.9</td>
<td>3.1</td>
<td>14.8</td>
</tr>
<tr>
<td>Personal Control</td>
<td>0.73</td>
<td>6-30</td>
<td>18.5</td>
<td>4.4</td>
<td>18.2</td>
</tr>
<tr>
<td>Illness Coherence</td>
<td>0.87</td>
<td>5-25</td>
<td>19.0</td>
<td>4.2</td>
<td>18.8</td>
</tr>
<tr>
<td>Emotion</td>
<td>0.86</td>
<td>6-30</td>
<td>16.5</td>
<td>5.4</td>
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α: Cronbach’s Alpha. F= MANOVA F statistic. η²=Partial effect size. **p<0.01
Figure 9.1: Means and 95% confidence intervals for the IPQ-R time-line and consequence scores, comparing adherent and non-adherent patients.

Table 9.3: Demographic and clinical correlates of % weigh gain.

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<th>Correlation</th>
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<th>4</th>
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<sup>a</sup>Spearman’s Rho. Bold indicates significance (p<0.05).
### Table 9.4: Psychological correlates with % weight gain.

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<th>Pearson's r</th>
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<td>.175</td>
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<td>.219</td>
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<tr>
<td>12 Causes Emotion</td>
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<td>-.111</td>
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<td>.010</td>
<td>.009</td>
<td>.026</td>
<td>.285</td>
<td>.244</td>
<td>.167</td>
</tr>
</tbody>
</table>

Bold indicates significance (p<0.05).

### 9.3.4 Logistic Regression:

In order to test the hypothesis that illness representations would predict a clinically relevant group of non-adherent patients, logistic regression was undertaken. Age, gender, KRU, dialysis vintage and urea were all entered into an initial model as control variables. Given that the distribution of KRU was skewed, and in-keeping with previous studies from the renal service at Lister Hospital, we defined patients as having some (≥1 ml/min), or minimal (<1 ml/min) KRU (Vilar, Wellsted, Chandna, Greenwood, & Farrington, 2009). Kt/V was not entered in the models as it was deemed not to be a predictor of fluid-non-adherence, rather a consequence of increased weight gain (i.e. longer dialysis sessions, t_d). This first model was significant as compared to a constant only model (Chi-square=29.8 df=5, p=0.0001, Nagelkerke R² =0.385, table 9.5). Gender, urea and KRU were all significantly associated with non-adherence. In a second model, BDI scores, illness identity,
time-line, consequence, personal control, cyclical perceptions and two causal items (germ and emotions) were entered. Treatment control was excluded due to inadequate internal reliability ($\alpha=0.44$), as was the IPQ-R emotion dimension as it correlated highly with the BDI. This second model was significant, and improved the model fit ($\Delta$Chi-square=20.4 df=8, $p=0.009$, Nagelkerke $R^2 =0.59$). This model demonstrated that after controlling for several clinical factors including KRU, perceived consequences significantly predicted non-adherence (table 9.5). Holding all variables constant, a 1 point increase in consequence perception scores, reduced the odds of non-adherence by approximately 25%. Gender was also a significant predictor of non-adherence, with females being 12 times more likely to be non-adherent, *albeit* with wide confidence limits.

Table 9.5: Logistic Regression models predicting fluid non-adherence.

<table>
<thead>
<tr>
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<th></th>
<th>Step 2 (Model 2)</th>
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<td></td>
<td>95% CI OR</td>
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<tr>
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<td>Causal Germs</td>
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<tr>
<td>Causal Emotion</td>
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</tbody>
</table>

*Step 1.* Model Chi-square=29.8 df=5, $p=0.0001$. Nagelkerke $R^2 =0.385$. Overall predicted correct 83.8%  
*Step 2.* Model Chi-square=50.3 df=13, $p=0.0001$. $\Delta$Chi-square=20.4 df=8, $p=0.009$ Nagelkerke $R^2 =0.59$. Overall predicted correct 86.9%. OR= Odds Ratio. DV= Adherence (yes/no).
9.4 Discussion

The aim of this chapter was to establish the potential utility of the CSM in explaining fluid non-adherence. Put another way, do fluid non-adherent patients hold different illness representations as compared to fluid adherent patients? Given the potential issues described previously, efforts were taken to define a clinically relevant group of non-adherent patients who would be at risk of fluid related complications. This included the consideration of dry weight and residual renal function. The results revealed that non-adherent patients reported significantly lower time-line perceptions as compared to the adherent, suggesting that these patients held weaker perceptions of illness chronicity. Past reports have also identified the importance of time-line perceptions upon self-care behaviour (Bucks et al., 2009; Meyer et al., 1985). The importance of consequence perceptions upon patient fluid adherence was identified in multivariate analysis. Lower consequence perceptions increased the odds of non-adherence in this patient group. This finding supports past studies which have shown that consequence perceptions are related to health related outcomes (Hagger & Orbell, 2003; Horne & Weinman, 2002; Petrie et al., 1996). For example, in a longitudinal assessment of rheumatoid arthritis patients, stronger consequence perceptions were associated with more outpatient clinic visits (Scharloo et al., 1999).

This evidence offered in this chapter supports the CSM in understanding health-related behaviour as applied to chronic illness states. However, as noted elsewhere (Stafford, Berk, & Jackson, 2009) consequence perceptions are similar to perceived severity perceptions outlined in the health belief model. Therefore the findings here may have also been replicated using alternative models of health behaviour. Critically however, the implication of measuring representations of disease and not attitudes regarding fluid restriction is important. To elucidate, the data described here may be explained in terms of self-regulatory failure or misregulation (Carver & Scheier, 1981), which may have an impact upon fluid intake behaviour. According to the CSM, coping is embedded in “IF-THEN” rules (Leventhal et al., 1998). The “IF” is the interpretation of the illness; “THEN” refers to the procedures adopted in response to the defined threat. “IF” the ongoing disease threat is not perceived as serious (i.e. low perceived consequences) then the need to adopt strict health care behaviour (i.e. fluid control) may not be highly salient to the individual. The IF-
THEN rules reflect a coherent self-regulatory system (Leventhal et al., 1998). Therefore it is speculated that non-adherent patients under-regulate this health behaviour based upon their definition and interpretation of their illness. However the role of coping in IF-THEN rules is unclear. While the CSM posits that coping produces should mediate the relationship between illness representations and health related outcomes, studies have failed to confirm this (Heijmans, 1999; Scharloo et al., 1998). Longitudinal studies examining illness representations and coping in ESRD patients seem highly relevant if we are to increase our understanding of the relationship between self-regulatory processes and outcome.

This is only the second empirical investigation to explore the utility of illness representations in respect to non-adherence among ESRD patients. O’Connor et al (2008) demonstrated that time-line perceptions predicted dietary adherence among ESRD patients, but failed to find any association with fluid adherence. Theoretically perceptions of control (or self-efficacy) should be important determinants of outcome in ESRD patients (Christensen & Ehlers, 2002). Indeed a previous study has shown that self-efficacy was related to fluid adherence, as assessed by a self report questionnaire (Zrinyi et al., 2003). However in the present analysis there was no evidence that perceptions of control differed between the adherent and non-adherent groups. These null findings may reflect the lack of specificity in the IPQ-R questions with regards to particular treatment behaviours (i.e. fluid control). Indeed it is suggested that self-efficacy is a powerful predictor of behavioural change and goal attainment (Bandura, 1977). As suggested earlier, it is likely that questions about treatment control in the IPQ-R were interpreted as “dialysis treatment control,” as this is the most salient regime to the patient when on-dialysis (see Chapter 5). As in other social-cognitive models asking about specific behavioural self-efficacy may have value (e.g. Theory of Planned Behaviour). For example in the Theory of Planned Behaviour, self-efficacy for a given behaviour has been shown to have a direct relationship with actual behaviour, and is independent of intention (Armitage & Conner, 2001).

In keeping with the ideas posited in the CSM, Horne and colleague’s developed the necessity-concerns framework regarding beliefs about medicines, which has shown to be important determinants of medication adherence (Horne, 1997; Horne & Weinman, 1999). The scope of applying the necessity-concerns framework to specific health behaviours such as fluid control may also bear fruit. For example, asking patients about how necessary they
think fluid control is, and exploring perceptions regarding the consequences and concerns of restricting fluid intake may be a useful aid in understanding the psychology of specific health behaviours. The elaboration of such models may be of further value given that treatment regimes encountered in ESRD and other chronic conditions are complex and multifaceted, and are likely to involve different antecedent factors.

The thesis of a recent review elegantly argued that self-regulatory efforts should integrate both affective and disease management elements (Detweiler-Bedell et al., 2008). To illustrate, although we suggest that lower consequence perceptions are associated with non-adherence, other empirical evidence suggests that consequence perceptions relate positively with psychological distress (Hagger & Orbell, 2003). Altering a particular cognition to improve health behaviour may have a negative impact upon psychological functioning, if the integration of affective and cognitive factors is not considered (Detweiler-Bedell et al., 2008). For example, a recent investigation revealed that greater perceived consequence perceptions were associated with poorer well-being in HD patients (Timmers et al., 2008), and data presented in previous chapters in this thesis suggest that illness perceptions are associated with depression in this patient group.

Of the demographic factors explored gender was a significant predictor of non-adherence. However the gender non-adherence association demonstrated in this study appears to oppose the direction found in past studies (Bame et al., 1993), as females were likely to be more non-adherent. We suspect that controlling for dry weight lead to these somewhat surprising findings; women tend to have a lower weight and a lower IDWG, and therefore would be underrepresented in non-adherence defined by IDWG compared to % weight gain (i.e. the amount of weight increased as a proportion of their ideal dry weight). Further, it appears that this finding was not confounded by KRU, as males and females have similar KRU. However, the confidence limits obtained were large, thus the effect of this finding should be taken with care.

It is acknowledged that this investigation had some limitations, the most significant being the cross-sectional design, which prevents the identification of temporal relationships. Our assessment of illness perceptions were time limited, whereas the clinical parameters were averaged over a period of time, although it is unlikely that over this short period illness
perceptions would alter significantly. A further consideration concerns the patient’s knowledge of renal failure and subsequent treatment, which was not measured. This limits the distinctions we can make between intentional and non-intentional non-adherence (Horne, 1997). However it is interesting to note that the knowledge of kidney disease did not predict adherence in a previous study (O’Connor et al., 2008). However given the increasing age of dialysis patients with known cognitive impairments, forgetting and a lack of comprehension are likely to contribute to non-adherence.

With regards to the IPQ-R, we used the original illness identity items and, due to our sample size could not use factor analysis on the causal items. Factor analysis is the preferred method of assessing the IPQ-R causal items, and promotes more meaningful results than exploring single items. Larger studies are needed to address these issues in order to confirm our findings. Further, our decision to define non-adherence, and compare groups, as opposed to assessing the variation in weight gain was pragmatic as we aimed to examine a clinically relevant group after considering dry weight. Additionally unlike past studies we did not exclude patients with urine volumes >500 ml/day. A number of patients still pass significant amounts urine, thus in order to improve the sample representativeness it was decided to control for residual renal function.

Despite the study limitations our data suggests that illness representations are associated with fluid non-adherence and should be further investigated with the scope for suitable intervention. A premise to this investigation regards interventional research that has shown that the modification of illness perceptions by psychological intervention leads to improvements in health related outcomes (Hall, Weinman, & Marteau, 2004; Petrie et al., 2002). Targeting maladaptive self-regulatory processes seem important if we are to improve adherence in ESRD patients (Christensen, Moran, Wiebe, Ehlers, & Lawton, 2002).
9.5 General remarks

This chapter has explored the illness representations that relate to fluid non-adherence. To surmise, the CSM has predictive utility in this context. The potential to improve non-adherence may be realised by targeting maladaptive illness cognitions. However, it is stressed that an integrative approach to disease management may be fundamental to such efforts as posited by Detweiler-Bedell et al (2008). The rationale is that a maladaptive cognition for treatment adherence may reflect an adaptive cognition for a positive psychological outcome (i.e. to repair mood see Detweiler-Bedell et al., 2008).

The final chapter of this thesis extends the clinical application of the research conducted so far by examining the association between depression and illness perceptions with mortality. Specifically, data is presented that examines the short-term survival of the incident cohort (chapter 8) and evaluates whether psychological factors predict mortality.
Chapter 10

Depression and illness perceptions as predictors of short-term survival in incident dialysis patients

10.1 Introduction

The final chapter in this clinical section addresses the relationship between depression, illness perception and mortality in incident ESRD patients. There is increasing evidence that depression is associated with adverse outcomes, including mortality among patients with physical disease. Particular attention has been devoted to the relationship between depression and cardiac disease and events (Steptoe, 2007). Indeed, it is well established that depression is associated with the development of cardiac diseases and events, recurrent events and death (Anda et al., 1993; Barefoot et al., 1996; Frasure-Smith, Lesperance, & Talajic, 1993; Lesperance, Frasure-Smith, Talajic, & Bourassa, 2002; Penninx et al., 1998; Rosengren et al., 2004). Furthermore depression is associated with mortality among other physical conditions including diabetes (Black & Markides, 1999) and stroke (Morris, Robinson, Andrzejewski, Samuels, & Price, 1993).

In the UK the age adjusted survival rate for incident dialysis patients over the first year of therapy is 89% (Ansell et al., 2008). While several factors have been associated with short-term survival in the UK incident dialysis population the effect of depression has not been assessed.

As reviewed in chapter 2 (see table 2.2), there is good evidence that depression predicts mortality in dialysis patients, after considering an array of demographic and clinical covariates. However some studies have produced null findings, which may be attributable to the various assessments of depression used, the statistical methods employed, the populations studied (incident vs. established populations), sample size, and possibly reverse causality (Boulware et al., 2006). Both Kimmel et al (2000) and Boulware et al (2006) treated depression in a time-varying manner and found a positive association between depression and mortality, but failed to find an association between baseline depression and all-cause mortality. Furthermore, Boulware et al (2006) demonstrated that in adjusted time-varying models, depression was associated in a three-fold risk of CVD related death,
and a two-fold increase in all cause mortality. However the affect for both all-cause mortality and CVD death was attenuated after incorporating a six month time lag into the analysis, suggesting the potential role of reverse causality (i.e. medical morbidity causing depression, rather than depression leading to worsening morbidity). Large cross-sectional studies (e.g. data from DOPPS) report significant associations between base-line depression and mortality, albeit using relatively unconventional methods of depression assessment (Lopes et al., 2002). More recently others have used formal diagnostic approaches, and report a significant association between MDD and mortality, yet failed to replicate this association when using self-report questions to assess depressive symptoms (Hedayati et al., 2008).

In a related area, authors have examined the relative association between Quality of Life (QoL, physical and mental functioning) and mortality in ESRD (DeOreo, 1997; Knight, Ofsthun, Teng, Lazarus, & Curhan, 2003; McClellan et al., 1991). A study of over 14,000 ESRD patients revealed that both physical and mental functioning predicted survival over a year follow-up (Knight et al., 2003). Moreover, a decline in these QoL parameters was associated with increased mortality risk, after controlling for the baseline scores. A recent investigation examined the relationship between QoL, risk of ESRD, and mortality (Tsai et al., 2009) in patients with CKD. The combined end-point of either time to first dialysis or death was predicted by physical and psychological domains of the WHO-QoL questionnaire, after controlling for several co-variates (Tsai et al., 2009). Although CKD is a different population to ESRD, these results suggest the poor QoL is a risk factor for adverse outcomes across the spectrum of chronic kidney disease.

The mechanisms behind the depression-mortality association are likely to be complex (see chapter 2). The measurement or assessment of depression in ESRD is confused with somatic symptoms of illness, thus depression may be a marker of sub-threshold disease. Others have proposed that the association is explained by non-adherence to medical regimes (Carney, Freedland, Eisen, Rich, & Jaffe, 1995), and changes in hemostatic (Berk & Plein, 2000) and immune functioning (Kimmel et al., 1993; Lett et al., 2004), which are particularly implicated in the pathogenesis of Coronary Heart Disease and Cardiovascular Disease which remain significant co-morbidities in patients with ESRD (chapter 2). Furthermore maladaptive health behaviours associated with depression may also underlie
the association between depression and mortality including alcohol abuse and physical inactivity (Camacho, Roberts, Lazarus, Kaplan, & Cohen, 1991) and smoking (Lehto et al., 2000).

10.1.1: Illness perceptions and mortality

The evidence presented earlier in this thesis supports the contention that illness perceptions predict depression in ESRD. Moreover among dialysis patients there is good empirical support for depression predicting mortality. Therefore, it could be hypothesized that illness perceptions would predict mortality in ESRD, and that depression would potentially *mediate* the relationship. Indeed, preliminary evidence suggests that illness perceptions are associated with survival in dialysis patients (van Dijk et al., 2009). This study found that after controlling for demographic and clinical factors, weaker treatment control perceptions predicted mortality, although depression was not considered in the analysis (van Dijk et al., 2009). While the authors suggest that illness perceptions may impact survival by reducing the motivation for adaptive health care behaviours, there seems to be a strong rationale that depression may mediate the association between perception and mortality. Indeed this would fit the tenets of the CSM, as illness perceptions may lead to maladaptive coping procedures that may serve as cognitive and behavioural vulnerabilities for depression. Alternatively the misregulation or under-regulation of an illness threat may have detrimental effects upon health-related outcomes (Baumeister & Heatherton, 1996; Baumeister et al., 1994; Carver & Scheier, 1981; Detweiler-Bedell et al., 2008). The underlying assumption is that self-regulatory strength is a limited resource and can become depleted (Baumeister et al., 1994; Carver & Scheier, 1981). The implications of this resource view of self-regulation suggests that regulating an illness threat may lead to the successful adoption of positive health care behaviours, yet the under-regulation of emotion (i.e. vulnerability for depression). Similarly successfully regulating mood may lead to the under-regulation of disease management (Detweiler-Bedell et al., 2008). For these reasons it seems pragmatic to explore both depression and illness perceptions in relation to mortality risk, in order to broaden the scope for understanding the processes underlying such relationships.
The data to be reported here assessed survival in incident dialysis patients who were followed up for an average of approximately 18 months. The aims of the investigation were:

1) To determine whether depression predicts mortality in this cohort after controlling for co-variates associated with premature death in ESRD including age, inflammation (CRP), albumin and co-morbidity.

2) To determine if illness perceptions predict mortality, and whether depression mediates this relationship.

10.2 Methods

10.2.1 Design and Patients:
The survival of incident dialysis patients recruited in the longitudinal investigation (n=160, see chapter 8) was assessed over the study period (May 2007-December 2009). HD and PD patients were approach and recruited into the study at a point soon after dialysis initiation (median vintage 30.5 days, min 1 - max 100 days). Patients were eligible for inclusion if the following criteria was met; i) no known significant visual or physical impairment that would prevent the completion of the questionnaires, ii) fluency in verbal and written English language, (iii) not hospitalised at the time of assessment, iv) had been receiving HD or PD for ≤3 months, and v) no cognitive impairment as indicated by an age adjusted score of<22 on the Mini Mental State Examination (Folstein et al., 1975). Baseline depression scores (BDI), illness perception scores (IPQ-R), demographic information, clinical data, and KPS scores collected as a part of the incident cohort (chapter 8) were used in the survival analysis.

10.2.2 Co-morbidity and functional performance
Co-morbidity was assessed using the criteria described in the general methods (chapter 4). For the purpose of this short-term survival analysis, patients were classified as having, 1) no-low co-morbidity or 2) moderate-high co-morbidity. Moderate-high co-morbidity was defined as having advanced disease in any one system, or the presence of cancer (see methods). Patients were also classified as independent (≥70) or dependent (<70) based upon their KPS (see chapter 4).
10.2.3 Clinical parameters

In addition to demographic factors, baseline clinical data was recorded from electronic medical records including; primary ESRD diagnosis, smoking status, blood haemoglobin, serum albumin and C-reactive protein (CRP). CRP was skewed therefore it was treated using a laboratory clinical cut-off (>5 vs. ≤5). Estimated GFR was calculated from serum creatinine concentrations at the time of dialysis initiation, using the modified MDRD equation (Levey et al., 1999). Depressive history was recorded, where depressive disorders were listed in the medical problem lists in patients’ medical record. Anti-depressant use at the time of assessment was also recorded. As in chapter 8, path to dialysis was defined as either planned or unplanned.

10.2.4 Outcome assessment

All cause mortality was the outcome measure, which was ascertained by active surveillance through the renal clinics by the local consultant nephrologist, who verified the date of death. Patients were censored if they received a transplant, were lost to follow-up, recovered renal function, or were still alive at the end of follow-up.

10.2.5 Survival Analysis

Group comparisons (differences between depressed [BDI ≥16] and non-depressed [BDI<16]) were assessed via parametric, and where appropriate, non-parametric inferential statistics including Independent t-tests, Mann-Whitney U tests, and Chi-Square analysis (Pearson’s and Fishers exact test where appropriate). This data is present earlier in this thesis (chapter 8).

Kaplan Meier (KM) plots, with log-rank tests, were constructed to examine differences in survival (in days) between groups of patients. This was repeated across several variables to determine which variables may contribute to survival in a multivariate Cox model. Survival was described in terms of the cumulative proportion (Standard Error, S.E) of patients surviving 18 months (540 days) post dialysis initiation. It was not possible to estimate median survival due to the limited number of events.

A series of Cox proportional hazards models evaluated the association between depression symptoms and survival in both unadjusted and adjusted models. Adjusted models
controlled for the following covariates; age, sex, albumin, haemoglobin, path to dialysis, moderate-high co-morbidity, CRP>5, and KPS<70. The co-variates were selected due to their univariate association with either survival or depression. Two sets of models were produced, one in which depression was treated as a continuous variable (total BDI scores), and the other where depression was treated as a categorical variable (employing a BDI≥16 to define depressed patients, see chapter 5).

A second series of Cox-models evaluated the association between illness perceptions and survival. Crude and adjusted models (controlling for the covariates described above) were evaluated. Depression-Adjusted models controlled for age, sex, albumin, haemoglobin, path to dialysis, moderate-high co-morbidity, CRP>5, KPS<70 and BDI scores. According to tests of mediation (Baron & Kenny, 1986), illness perceptions that predict mortality should become non-significant after controlling for depression, if depression mediates the relationship between illness perception and survival.

10.3 Results

One hundred and sixty initiating dialysis patients completed the BDI soon after dialysis initiation and were followed up for median of 511 days (min 47- max 1027 days), during which there was 27 deaths (16.9%). Over the study period 4 patients recovered renal function, 14 became lost to follow-up and 14 were transplanted. Two patients died within 90 days of dialysis initiation, all survived at least 30 days. The cumulative survival at one year post dialysis initiation was 87.7% (S.E= 0.03), and at 18 months 85.9% (S.E=0.03). The mean age of the incident cohort was 57.4 (±16.0) years. The majority of patients were male (67.5%) and white (90.6%). Approximately one in four patients (25.6%) scored ≥16 on the BDI, and 15% had a documented history of depression in their medical records. Seventeen patients (10.6%) were on anti-depressants.

Differences between depressed patients (BDI≥16) and non-depressed (BDI<16) patients, with regards to baseline demographic and clinical factors were presented earlier as apart the longitudinal study (see results in chapter 8). Depressed patients were significantly younger and were more likely to have an unplanned entry to dialysis as compared to the non-depressed. In addition depression was significantly associated with dependent physical functioning (KPS<70), and with a depressive history. There was no difference between the
co-morbidity groups (none-low vs. moderate-high) with regards to BDI scores (11.9 ±9.3 vs. 12.3 ±7.7, t(158)=0.318, p=0.751). As shown in chapter 8, baseline BDI scores failed to correlate significantly with albumin, Hb, CRP, and dialysis vintage.

10.3.1 Univariate Analysis: Kaplan Meier survival functions with log-rank tests

There was a significant difference in survival between depressed (BDI ≥16) and non-depressed (BDI<16) patients (p=0.013, figure 10.1). At 18 months the cumulative survival (CS) in depressed patients was 74.9% (SE=0.07) compared to 89.6% (SE=0.03) in the non-depressed group. Functional status had a significant bearing upon survival (figure 10.2), with patients scoring KPS >70 surviving significantly longer (CS at 18 months= 90.6% SE=0.03) as compared to those with a KPS ≤70 (CS at 18 months= 58.5% SE=0.11, p<0.01). The cumulative survival at 18 months in patients with CRP>5 was 77.6% (SE=0.05) compared to 95.8% (SE=0.02) in those with CRP≤5 (figure 10.3), which was a significant difference (p=0.001). Survival functions defined by co-morbidity group are shown in figure 10.4. Moderate-high co-morbidity was associated with reduced survival (CS at 18 months = 76.1% SE=0.06) compared to none-low co-morbidity (CS at 18 months = 91.6% SE=0.03, p=0.001). Survival was not associated with any of the following factors, depressive history (p=0.474), diabetes (p=0.302), treatment modality (p=0.302), anti-depressant use (p=0.08), gender (p=0.486), and renal service (p=0.731). There was an effect of the path to dialysis upon survival tending towards significance, with unplanned starters having shorter survival (p=0.059, figure 10.5). The 18 month cumulative survival in unplanned patients was 77.0% (SE=0.07) compared to 89.3% (SE=0.03) in planned patients.

10.3.2 Cox-survival models: Depression and mortality

In unadjusted Cox-proportional hazard models, the BDI was significantly associated with mortality, with a one point increase in BDI increasing the hazard of death by 6% (table 10.1). The BDI remained significant after controlling for age and sex, and in fully adjusted models which controlled for the variables described in the methods (see table 10.1). A one point BDI increase was associated with an 8% increase in the hazard for death. This equates to approximately twice the risk of death for a 1 standard deviation change in the BDI. The results were replicated after substituting the continuous BDI scores with a BDI ≥16 to categorise depressed patients (vs. non-depressed, BDI <16). In a fully adjusted model
patients with a BDI ≥16 had a 2.4 increase in the hazard for death as compared to patients with a BDI<16 (p=0.05, figure 10.6).

Table 10.1: The association of depression symptoms with all cause mortality.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Crude</th>
<th>Age-Sex Adjusted</th>
<th>Fully Adjusted(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>1.06 (1.03 - 1.10), p=0.001</td>
<td>1.08 (1.04 - 1.10), p&lt;0.001</td>
<td>1.08 (1.03 - 1.13), p=0.002</td>
</tr>
<tr>
<td>BDI ≥ 16(^b)</td>
<td>2.58 (1.19 - 5.63), p=0.017</td>
<td>2.90 (1.31 - 6.32), p=0.009</td>
<td>2.40 (1.0 - 5.80), p=0.05</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted for age, sex, albumin, haemoglobin, path to dialysis, moderate-high co-morbidity, CRP>5, KPS<70

\(^b\)Where reference category (1.0) was non-depressed (i.e. BDI<16).

### 10.3.3 Cox-survival models: Illness perceptions and mortality

All of the illness perceptions were entered individually into crude Cox survival models to examine any associations with mortality. Only two illness perceptions showed a significant relationship with mortality, namely treatment control perceptions and illness coherence. In both crude and adjusted models, treatment control and illness coherence predicted survival (table 10.2). In depression-adjusted models (controlling for BDI scores) illness coherence was no longer a significant predictor of survival, whereas treatment control remained significant. This suggests that depression mediates the association between illness coherence and mortality. A one point increase in treatment control perceptions was associated with a 14% reduction in mortality risk. As with the previous Cox survival analysis (section 10.3.2) BDI score was also a significant predictor of mortality (HR=1.06 95% CI 1.01 – 1.11, p=0.02).
Fig 10.1: Survival functions for depressed (BDI ≥16) vs. non-depressed (BDI<15) patients (p=0.013).

Fig 10.2: Survival functions for functional performance (KPS) KPS>70 vs. KPS≤70 (p<0.001).

Fig 10.3: Survival functions for patients with a CRP ≤5 vs.CRP>5 (p=0.001).

Fig 10.4: Survival functions for patients with none-low vs. moderate-high co-morbidity (p=0.001)

Fig 10.5: Survival functions for patients with a planned vs. unplanned start to dialysis (p=0.059)

Fig 10.6: Adjusted* Survival functions comparing depressed vs. non-depressed patients (p=0.05)
Table 10.2: The association of illness perceptions with all cause mortality.

<table>
<thead>
<tr>
<th>Type of analysis</th>
<th>HR (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
</tr>
<tr>
<td>Treatment control</td>
<td>0.86 (0.77 – 0.98), p=0.02</td>
</tr>
<tr>
<td>Illness Coherence</td>
<td>0.90 (0.84- 0.98), p=0.01</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, albumin, haemoglobin, path to dialysis, moderate-high co-morbidity, CRP>5, KPS<70 and Illness coherence. ¥ Adjusted for age, sex, albumin, haemoglobin, path to dialysis, moderate-high co-morbidity, CRP>5, KPS<70 and treatment control. ~Adjusted for all the factors just described and BDI scores.

10.4 Discussion

There is convincing published evidence that depression is associated with adverse clinical outcomes among patients with physical diseases. However while there is a similar consensus within the ESRD literature, some studies have provided null findings, and there is heterogeneity with regards to the size of the effect. Furthermore, studies have varied in their methodological approach, and there is no UK data. Given this, a meta-analysis of the association between depression and mortality in ESRD seems highly relevant.

The data from this incident cohort reveals that the presence of depressive symptoms soon after dialysis initiation is associated with short-term survival. This finding supports data from previous research, which have utilised different statistical approaches and assessments of depression. As described earlier both Boulware et al (2006) and Kimmel et al (2000) failed to find an association between baseline depression and survival yet report an effect after depression was treated as a time-varying component. Lopes et al’s (2002) analysis of the DOPPS cohort found that two simple questions relating to mood (at baseline) predicted survival, although this was not an incident cohort. After using a conventional assessment of depressive symptoms, the data here demonstrates that baseline depression predicts short-term survival after adjusting for covariates including, albumin, path to dialysis and co-morbidity. These findings were not dependent upon how
the BDI scores were treated, either as a continuous variable or as an adjusted BDI cut-off score (BDI ≥16); both methods yielded a significant association between depression and mortality.

Depression and co-morbidity share a close relationship, thus the finding that depression predicts mortality may be confounded by co-morbidity; or that even the assessment of depression is a surrogate marker for co-morbidity. Although the data here, and in past reports suggest that the effect of depression is independent of co-morbidity, the study by Boulware et al (2006) suggest that worsening co-morbidity leads to increased depression rather than vice versa. As reported earlier, there was no evidence of an association between co-morbidity and depression, however it should be noted that co-morbidity was treated as a categorical variable in order to define a group of at risk patients (Chandna et al., 1999). Depression may have also been related to sub-threshold disease or to diseases not deemed to be high risk. Other explanations underlying the depression-mortality relationship include non-adherence (Carney et al., 1995), poor lifestyle (Ziegelstein et al., 2000), malnutrition (Koo et al., 2003), alterations to immune functioning (Kimmel et al., 1993; Lett et al., 2004), and increased platelet activation (Berk & Plein, 2000). Hypoalbuminemia, a known risk factor for mortality in ESRD (Leavey, Strawderman, Jones, Port, & Held, 1998) has also been associated also with depression in ESRD (Koo et al., 2003). No association between depression symptoms and albumin was found here, although it has been found that depression predicts decreasing serum albumin over time (Friend, Hatchett, Wadhwa, & Suh, 1997). Furthermore others report an association between depression and inflammation in ESRD patients (Simic Ogrizovic et al., 2009), although there is mixed evidence (Dervisoglu et al., 2008) highlighting the need for further empirical study. CRP was not associated with depression here, however it is likely that more specific markers like IL-6 and hsCRP are more appropriate. There is evidence of a association between malnutrition, inflammation, and atherosclerosis (MIA) in ESRD patients (Honda et al., 2006; Wang et al., 2004), and some preliminary evidence suggests that depression could be involved in MIA syndrome (Simic Ogrizovic et al., 2009), albeit with a great need for further investigation. Of further interest is residual renal function (Vilar et al., 2009) which has been show to predict survival in haemodialysis patients, and may be associated with depression (Chilcot, Wellsted, Vilar, & Farrington, 2009). A paper
describing the association between depression and residual renal function can be found in the appendix (Chilcot et al., 2009).

As presented earlier (chapter 8) depression symptoms are greater in patients who have an unplanned start to dialysis. A Kaplan-Meirer plot with a log-rank test demonstrated a near significant association between an unplanned start to dialysis and mortality which confirms previous data (Chandna et al., 1999); although the relationship was non-significant in adjusted Cox model. The inclusion of depression, albumin and co-morbidity in the adjusted model may mediate the relationship between unplanned path and mortality, although further investigation is required to confirm this assumption.

While the discussion to this point has focused upon the depression-mortality association, the secondary aim of this investigation was to determine if illness perceptions predicted mortality. One previous study found that lower treatment control perceptions predicted mortality in ESRD (van Dijk et al., 2009). The data reported here revealed that both lower treatment control perceptions and weaker illness coherence (illness understanding) predicted mortality after controlling for demographic and clinical variables. However unlike the van Dijk study, depression was controlled for in subsequent “depression-adjusted” models. After adjustment the relationship between illness coherence and mortality was attenuated, while the BDI total score remained associated with mortality. This suggests that the association between illness coherence and mortality is mediated by depression. Treatment control perceptions remained a significant predictor of mortality even after controlling for depression scores, suggesting that illness perceptions and depression can have independent effects upon survival. This notion is in accord with the tenets of the parallel response model described in chapter 3 (Leventhal, 1970). Lower treatment control perceptions may be associated with survival due to behavioural factors such as non-adherence. In chapter 9 treatment control was not a significant predictor of fluid adherence, although as discussed previously non-adherence is multifaceted in ESRD. Lower treatment control may be associated with other maladaptive health behaviours in ESRD which may add to the explanation of this mortality-association.

Following dialysis initiation, efforts are made to correct ESRD related problems including problems relating anaemia, and bone and mineral metabolism. The data presented here
indicates that the treatment of co-morbid depression and altering maladaptive illness perceptions may be helpful during this early period. As eluded to earlier in this thesis (chapter 2), there is there is mixed evidence that treating depression has a positive impact on survival and outcomes in physical illnesses (Detweiler-Bedell et al., 2008), even though treatment may have an important role in improving quality of life. The data shown here supports the thesis of Detweiler-Bedell et al (2008) who propose an integrated approach of depression and disease management in order to avoid self-regulatory failure and maladaptive outcomes (Baumeister & Heatherton, 1996; Baumeister et al., 1994). While it is clear that illness perception and depression share a dynamic relationship, the data shown here argues the case that mood and perceptions can have independent effects upon survival outcomes.

The study here did have a few limitations which are worthy of discussion. Although we employed a conventional depression severity tool (and used an adjusted BDI cut-off for ESRD patients), recent evidence questioned the association between depression, as assessed by questionnaire methods, and mortality, instead reporting an effect only with a diagnostic scheme for MDD (Hedayati et al., 2008). Future studies should utilise diagnostic assessment for MDD in order to identify whether the mortality association is upheld. There was also some heterogeneity as to the time when patients were assessed post dialysis initiation. However the data shows that there was no relationship between dialysis vintage and depression symptoms, therefore it appears that the time since dialysis initiation during the 3 month recruitment window did not have an undue influence on the relationship between mood and mortality. A further limitation regards the assessment of depressive history. Relying on a documented history is likely to under represent depressive history, particularly as depression is often under recognised in this patient population (Wang & Watnick, 2004). However the impact of depressive history may not be all that important, as research into patients with a recent MI suggest that it is post and not pre-MI depression that is predictive of future cardiac events and death (Dickens et al., 2008; Grace, Abbey et al., 2005). With regards to the treatment of co-morbidity our approach differed from others. Given the relatively short follow-up it was important to define a group of patients who were at high risk over this period. While the findings did not change when using alternative methods including the Davies method (Davies et al., 2002), the current method
was preferred because it was a stronger predictor of mortality in the adjusted Cox proportional hazard models.

10.5 General remarks

Data has been presented in this chapter that demonstrates a significant risk of death for patients with depressive symptoms shortly after dialysis initiation. This is the first UK data that has examined the impact of depression upon survival and adds to the wider body of literature. Moreover illness perceptions are associated with mortality which supports one other study in ESRD. Increasing our understanding of the pathways between depression, illness perception, and mortality in ESRD may help better define and develop integrated interventions to attenuate the risk of depression and death, and thus improving the psychological and clinical sequel of dialysis patients.
Chapter 11

General Discussion

11.1 Overview

The evidence presented in preceding chapters is offered to defend the thesis-

*Depression is a common psychopathology in patients with End-Stage Renal Disease that is associated with maladaptive illness representations. Moreover depression and illness representations predict adverse outcomes in End-Stage Renal Disease.*

In summary the investigations have established several novel findings:

1) On-dialysis depression screening is a viable procedure for the assessment of depression. Furthermore a BDI score of $\geq 16$ compares well with a diagnostic method for Major Depressive Disorder in ESRD patients.

2) The factor structure of the BDI used with ESRD patients is best understood in terms of a bi-factor measurement model.

3) Illness perceptions are strongly associated with depression in dialysis patients and predict the trajectory of depression over the first year of dialysis.

4) Clinical variables are largely unrelated to depression in ESRD; rather it is the interpretation of the condition via illness representations that is more fundamental.

5) Illness perceptions explain fluid non-adherence in ESRD patients.

6) Depression and illness perceptions predict short-term survival among incident dialysis patients.

11.2 Consideration of methodology: Assessing depression in ESRD

In order to achieve the aims of the empirical work presented, careful consideration of the methodology was required. Accordingly two studies were devoted to the evaluation of the methods (chapters 5 & 6). This was particularly important for several reasons. Firstly it was important to establish a practical procedure for assessing patients. Since the majority of patients recruited in the studies would be receiving in-hospital haemodialysis it seemed
sensible for them to complete the BDI and IPQ-R while on-dialysis. Furthermore screening for depression while on-dialysis has potential implications for regular screening in routine practice, particularly since depression remains a common yet under recognised psychopathology (Wang & Watnick, 2004). Finally the issues of measuring depression among patients with chronic illnesses are well documented (Cavanaugh et al., 1983; Koenig et al., 1997), thus establishing the validity of the BDI in UK ESRD patients was of importance.

The results from the pilot study of chapter 5 suggest that on-dialysis depression and IPQ-R assessments are viable and lead to similar responses made by the same individuals assessed off-dialysis. On-dialysis assessments were employed for all haemodialysis patients in the subsequent studies, therefore providing a standardised method of assessment.

Interestingly, there was a slight bias for higher scores on the somatic items of the BDI when on-dialysis as compared to off-dialysis. If used regularly as a screening tool in clinical practice, on-dialysis screening would potentially produce more false positive screens for depression, yet would capture more patients and thus reduce false negative cases. With regards to defining a relevant BDI cut-off score for depression, scores were compared against a diagnostic interview conducted as part of the assessment. First and foremost it was clear, as others have reported, that BDI cut-offs require adjustment in ESRD patients (Grant et al., 2008; Watnick et al., 2005). The results here revealed that a BDI≥16 had optimal sensitivity and specificity for major depression. These findings support the results of Watnick et al (2005), although it remains important to distinguish the original BDI as used by Watnick et al and indeed others (Craven et al., 1988) with the BDI-II as used here.

The factor structure of the BDI was the focus of chapter 6. Several proposed factors for the BDI are suggested in the literature, and were evaluated by confirmatory factor analysis from data pooled between longitudinal and cross-sectional investigations presented in this thesis. The best fitting model, as determined by absolute fit indices, was found to be a bi-factor measurement model as suggested by Ward (2006). This analysis is the first to evaluate the underlying factor structure of the BDI in ESRD patients, and has substantial implications for how others have treated BDI data by using a cognitive subscale (CDI, Kimmel et al., 2000; Sacks et al., 1990). As previously articulated in chapters 2, 3 and 6, the
CDI was never derived via factor analysis. There was little evidence from the CFA conducted in chapter 6 that distinctive cognitive and somatic factors (e.g. two factor models) explain the underlying measurement structure of the BDI in this patient context. Rather, a general depression factor was supported accompanied by two orthogonal cognitive and somatic factors (Ward 2006). Taken together it is possible to separate the variance from a general depression factor in order to form cognitive and somatic factors although these individual factors contribute little unique variance to the measurement model above and beyond “general depression”. It is therefore appropriate to utilise the BDI (total score) as a global measure of depression as was done in the analysis of chapter 8. It is also possible to utilise the measurement model defined in chapter 6, particularly if researchers are interested in evaluating predictors that explain unique variance in the cognitive or somatic factors of the BDI.

In summary, the first empirical section devoted a substantial amount of consideration to the methodology particularly the measurement of depression. In doing so the factor structure of the BDI for use with ESRD patients was best defined, a procedure of on-dialysis assessment evaluated, and an adjusted BDI cut-off identified for use within the UK renal population.

11.3 Illness Representations and Depression in ESRD

The second empirical section examined the cardinal feature of this thesis, namely the relationship between depression and illness representations. In both the cross-sectional and longitudinal studies, depression as estimated by a BDI cut-off score ≥16 was highly prevalent (29% and 26% respectively). These estimates are similar to those found elsewhere (Hedayati et al., 2008; Kimmel et al., 2000) and reaffirm that depression is the most common psychopathology in ESRD patients.

The CSM of illness representations posits a dynamic self-regulatory system that attempts to resolve or manage illness threats (Leventhal et al., 1980; Leventhal et al., 1984). Accordingly, core features of the representation namely illness perceptions (identity, timeline, consequences, control and causes) accompanied by a parallel emotional response serve as the psychological interpretation of the illness state. Illness representations guide the selection, maintenance and adaption of coping procedures, employed to tackle the
illness threat. Furthermore the CSM posits that following coping efforts, appraisal of the outcomes is undertaken which inform new targets for regulation, or continued regulation, of the current state by updating the representation or coping procedures. However, it should be noted that the appraisal process defined in the CSM has received little empirical attention. Furthermore there is limited support that coping mediates the association between illness representations and outcomes (Heijmans & de Ridder, 1998; Scharloo et al., 1998). Nevertheless, as reviewed in chapter 3 it is clear that illness representations are associated with psychological and functional outcomes (Bijsterbosch et al., 2009; Hagger & Orbell, 2003; Juergens et al., 2010). Furthermore there is evidence that specific illness perceptions (in particular consequences and timeline) predict depression in both cross-sectional and longitudinal studies. However, there are notable differences within the literature with regards to the assessment of depression, study designs and statistical methodologies. A meta-analysis on the topic would therefore be of considerable value.

Chapter 7 is the first study to investigate the relationship between illness representations and depression in ESRD patients. Indeed the results demonstrated an association between depression and several illness perceptions. Furthermore, depressed individuals as defined by a BDI ≥16 were characterised by different illness perceptions as compared to the non-depressed. Perceptions of lower control, greater consequences and lower coherence predicted depression in established HD patients. These findings agree with the results in other illness groups (Jopson & Moss-Morris, 2003; Schiaffino et al., 1998), suggesting that it is the interpretation and regulation of illness that serve as vulnerabilities for depression among patients with chronic illnesses. Chronic illness and its interpretation through illness representations are likely to perpetuate negative cognitions that are associated with depression. Indeed individuals with chronic physical disease are likely to have lower self-esteem and locus of control as compared to healthy controls (Bailis & Chipperfield, 2002; Leung & Bryant, 2000). Illness representations may increase the vulnerability for depression by activating negative depressive schema or by maladaptive self-regulation as posited in the CSM (Detweiler-Bedell et al., 2008). The under regulation of mood and subsequent failure to “repair mood” may occur as a direct consequence of the regulation of the disease state (Detweiler-Bedell et al., 2008). Put simply, focusing on the regulation of the disease
state may help attain disease related goals, but to the detriment of mood due to the failure to invest attention and self-regulatory effort to mood repair.

The longitudinal study of chapter 8 corroborated the findings of chapter 7. At baseline illness perceptions were associated with depression. What is of specific interest is the novel finding that path to dialysis was associated with illness perceptions, and in structural equation modelling illness perceptions mediated the association between path to dialysis and depression. This suggests that individuals with an unplanned start to dialysis held a different interpretation of their illness, and presumably different targets for self-regulation. It is therefore likely that unplanned patients were attempting to regulate aspects of the disease management, particularly as they reported lower illness coherence and greater unpredictability. As articulated above, the attention unplanned patients may have devoted to self-regulation of the illness, may have lead to the under regulation of mood as evidenced by increased depression scores. Although somewhat speculative, such an explanation does conform to current perspectives in the regulation of health and illness, albeit with a need to further address the dynamics of regulation pertaining to chronic disease.

Evaluating the data over time revealed relative stability in depression and illness perceptions. There was a tendency for the BDI to decline over the follow-up as determined in an unspecified latent growth model. Examination of individual BDI trajectories suggests however, that there may be some patients who remain stable over time, and others who improve or worsen over time. An appropriate method of identifying different clusters of trajectories is latent class growth analysis (Nagin & Odgers, 2010). However, this could not be undertaken here because of a relatively small follow-up and sample size. Taken together, there appears to be some change in mood over the first year of dialysis therapy, yet further empirical investigation is required in order to identify its function.

Examination of the IPQ-R dimensions in latent growth models revealed that illness identity decreased over time, and illness coherence strengthened (i.e. improved). This implies that patient’s illness identity based upon symptoms attributed to ESRD is reducing, whilst their illness understanding is increasing over time. Others report larger differences in illness perceptions over time (Bijsterbosch et al., 2009; Fischer et al., 2010; Lawson et al., 2008)
however it is likely that the disease specific nature of the condition is largely responsible for these larger differences. For example, following an acute MI, illness perceptions may change over time as individuals move from the “illness state” into the “recovery state”. In chronic conditions like the ESRD the illness state remains constant, although in some conditions like RA, cyclical symptomatic events can occur that may potentially lead to altered perceptions. Indeed, Heijmans et al (1998) highlight differences between disease groups with regards to illness perceptions, yet few studies have followed suit. Such comparisons may provide good opportunities to test specific theories relating to the change in illness perceptions over time between patient populations.

A central consideration in chapter 8 was establishing the predictors of the change in depression over the first year of dialysis using latent growth modelling. LGM is particularly suited to this kind of analysis, yet few researchers have attempted this method to examine the trajectory of depression in chronically ill populations. The findings suggested that baseline timeline and emotional reaction predicted a significant change in depression over time. Greater timeline perceptions at baseline predicted an increase in depression over time. Indeed this finding supports those from other studies suggesting that chronicity perceptions are particular cognitions associated with depression that may reflect feelings of hopelessness. Furthermore stronger timeline perceptions may have been associated with different regulatory goals, which as posited previously, may have led to insufficient mood regulation. An interesting additional observation was that greater emotional representations at baseline were associated with reduced depression symptoms over time. This may reflect some regression towards the mean phenomena, or alternatively suggest that greater baseline distress promoted attention to the regulation of mood resulting in improved depression scores over time (i.e. mood repair).

In summary, the second empirical section has provided support for the cross-sectional association between depression and illness representations, and has also shown that illness representations are associated with the trajectory of depression among incident dialysis patients.
11.4 Illness Representations and health behaviour

The final empirical section attended to clinical outcomes in dialysis patients. The first study in this section investigated the predictors of fluid non-adherence, taken to mean poor adherence to dietary salt and water restriction since fluid intake is driven by thirst which is closely linked to salt intake. Fluid restriction is just one facet of the ESRD treatment regime, in which non-adherence remains a significant concern. Failure to adequately control the intake of fluid can result in adverse clinical outcomes including hospitalisation and death, thus understanding the psychology of this behaviour is highly relevant. As highlighted within the literature non-adherence is conceptually hard to define and indeed measure. Therefore substantial effort was devoted to defining a group of patients with clinically significant fluid gain (IDWG, measured as a proportion of their ideal dry weight). Previous studies have failed to consider residual renal function (e.g. O’Connor et al., 2008) which may be a significant confound when defining non-adherence based upon weight gain. In the investigation of chapter 9, residual renal function was measured and controlled for in the analysis in an attempt to better define predictors of non-adherence.

The findings of chapter 9 are the first to show that illness perceptions predict fluid non-adherence in HD patients. This observation supports published data which reports an association between illness perceptions and maladaptive health care behaviours (Cooper et al., 1999; French, Cooper, & Weinman, 2006; Nouwen, Urquhart Law, Hussain, McGovern, & Napier, 2009). While more proximal perceptions pertaining to the actual behaviour (i.e. attitudes, treatment cognitions and self-efficacy) are likely to be important, the data here suggest that self-regulatory processes surrounding the interpretation of the illness can influence health behaviour. Indeed this notion is capsulated in the CSM operationalised as “IF THEN” rules, which are presumed to be embedded within the illness schema (e.g. Henderson et al., 2009). If the condition is not perceived to be as serious, then particular strategies or behaviours may not be salient to the individual and thus deemed not to be important.

A limitation of chapter 9 is the cross-sectional design, which prevents temporal associations from being made. While it appears theoretically appropriate that illness perception should influence subsequent behaviour, it is plausible that non-adherent behaviour, and indeed “getting away with it”, may influence illness perceptions. Examining the temporal
association between illness perception and non-adherence would be of value, particularly considering an array of ESRD health behaviours including dialysis attendance and phosphate control.

11.5 Clinical Outcomes

The final chapter provided an evaluation of depression, illness perceptions and short-term survival among incident dialysis patients. The data here demonstrated that depression symptoms at a point soon after dialysis initiation predicted short-term survival, after controlling for potential co-variates including co-morbidity and age. Previous studies have also reported an association between depression and mortality in ESRD patients (Hedayati et al., 2005; Kimmel et al., 2000; Riezebos et al., 2010), yet it is my understanding than none have examined short-term survival in incident patients.

Interestingly an evaluation of illness perceptions revealed that treatment control perceptions predicted mortality, an effect that was upheld even after controlling for depression. In addition illness coherence was found to predict mortality; however the effect was attenuated after controlling for depression, suggesting the depression mediated the association.

In conclusion it has been demonstrated that greater depression symptoms and weaker perceptions of treatment control are predictors of survival among incident dialysis patients. While the mechanisms underlying these associations are not fully understood, non-adherence and other maladaptive health behaviours appear obvious explanatory candidates. The quote provided at the beginning of chapter 2 appears extremely apt with regards to these data,

“If you be sick, your own thoughts make you sick”

- Benjamin Jonson (1572-1637)
Taken together the final empirical section offers evidence that illness representations and depression are associated with adverse clinical outcomes in dialysis patients, thus the potential to improve the clinical sequel of patients by altering perceptions and treating depression remains substantial.

11.6 Empirical Limitations

It is acknowledged that the work here suffered some general limitations. Throughout the thesis depression symptoms were assessed using a severity measure and not by a diagnostic method. While assessing the relationship between illness perceptions and Major Depressive Disorder would be of interest, it was beyond the scope and practicalities of the investigations here. Adopting this approach would have certainly led to smaller sample sizes in the investigations reported due the fact that diagnostic enquiries cannot be easily conducted on-dialysis. Further, solely considering a diagnosis would have restricted the evaluation of the depression over time, which is better suited to the use of continuous data. Nevertheless examining illness perceptions in patients who meet a diagnosis of MDD would shed further insights into the relationship between perception, regulation and mood in ESRD. However it is envisaged that similar findings would be observed if diagnostic approaches were employed, as similar illness perceptions were associated with depression in the analyses here that treated depression both as a dichotomous variable (BDI≥16) and a continuous severity score.

With regards to the patient demographic, the studies here were mostly restricted to HD patients. While the longitudinal study did include a sample of PD patients, comparisons between treatment modalities was not the main focus in these studies. However there does appear to be a literature bias for studying the psychosocial aspects of patients on HD and not PD, despite the fact that PD may offer several advantages with regards to Quality of Life (Brown et al., 2010). Extending the work here to include a representative PD patient sample would be of value, particularly as it would allow treatment specific differences in depression and illness representations to be identified and modelled over time.

Although not of direct empirical interest here, it is acknowledged that some measure of coping may have added to the explanation of data presented, particularly in the studies that utilised SEM approaches. This would have allowed specific assumptions of the CSM to
be tested. However there is a growing literature that shows that coping does little to explain the association between illness perception and outcomes. While it is probable that conventional conceptualisations of coping may be inappropriate or even overlap with illness perceptions, it is clear that researchers need to define the specific mechanisms involved (e.g. coping procedures) that allow illness perceptions to translate into behaviour and outcomes.

A final consideration concerns the IPQ-R. The symptoms that made up the identity subscale and the causal perception items were taken from the original questionnaire. Tailoring these items so there were renal specific may have better captured renal specific identity and causal attributions.

11.7 Future Directions

It is clear from the evidence presented in this thesis that depression is a significant extra-renal co-morbidity that requires recognition and treatment, particularly given its association with increased mortality. Depression appears to be similar to other extra-renal co-morbidities because it requires some level of vulnerability and an activating event (stress or illness accompanied by its interpretation, c.f. Beck et al., 1967). Therefore like other co-morbidities it requires detection and management in ESRD patients. Accordingly initially work should be undertaken in order to test whether regular depression assessment increases diagnosis and referral for treatment. With regards to the later, future trials are needed to evaluate interventions to treat depression, particular at a point soon after dialysis. Currently there is no suitably powered RCT of anti-depressants in ESRD and only one trial of CBT (Duarte et al., 2009).

While conventional treatments for depression including pharmacological and CBT interventions may be effective, the data presented here suggest the utility of targeting maladaptive illness representations. Indeed early work in the cardiac literature has shown the benefits of targeted illness perception inventions upon health related outcomes (Broadbent et al., 2009; Petrie et al., 2002). It is suggested that changing maladaptive illness perceptions early in the patient’s dialysis career could ultimately bring about lasting benefits with regards to mood and health care behaviour. Future interventions should ideally evaluate the potential benefits upon mood, behaviour and clinical outcomes. While
it is acknowledged that current research has not been able to consistently show that treating depression improves clinical outcomes, or have not directly tested the benefits upon clinical outcomes, it is envisaged that *integrating* depression and disease management strategies may help identify failures in self-regulation (Detweiler-Bedell et al., 2008). Adopting this approach may help promote increased quality of life and improved outcomes in ESRD patients.
References


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Appendix

A - Revised Illness Perception Questionnaire (Moss-Morris et al., 2002)

B- Beck Depression Inventory-II (Beck et al., 1996)

C- Patient Questionnaire

D- National Research Ethics Service Approval

E- Journal Papers