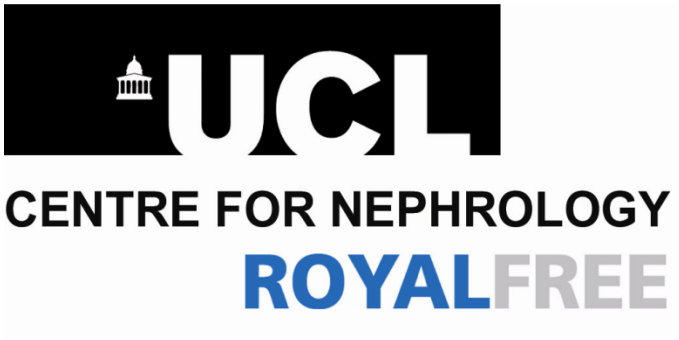

Psychosocial Distress in Older Patients with Advanced Chronic Kidney Disease

Dr Helen Alston

2018

A thesis submitted to University College London in fulfilment of the requirement for the degree of Doctor of Philosophy

1 Declaration

I, Helen Alston, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature

Helen Alston — 9th November 2018

Name — Date

1.1 Abstract

Background CKD disproportionately affects older patients, and survival in older renal patients is known to be poor. Older renal patients also report high symptom burden and poor quality of life.

Distress has been described as "the negative emotional experience of the individual" (National Comprehensive Cancer Network, 2010). It is a deliberately broad term, recognising that the causes of distress can be manifold.

Roth et al (1998) developed a simple tool, the **Distress Thermometer** (DT), to identify distress associated with unmet need in cancer patients. The aim was to enable staff, who may often concentrate solely on physical health issues, to consider and discuss with patients their psychological and social needs. It has been used in many diverse settings, however it has not yet been validated for use in renal patients.

Objective of this thesis To explore the phenomenon of distress in renal patients

Study 1 We compared the Distress Thermometer to four other screening tools in frequent use in renal patients: the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory II (BDI-II), the Memorial Symptom Assessment Scale (MSAS-SF), and the SF-36 quality of life assessment tool. Receiver Operator Characteristic analysis was used to compare the DT with the HADS and BDI-II, and sensitivity and specificity were calculated. We found high levels of agreement between the Distress Thermometer and the HADS and BDI-II depression screening tools (AUC 0.76 and 0.87 respectively), correlation between high DT scores and high symptom burden on the MSAS-SF, and an inverse correlation between all subscales of the SF-36, in particular the Energy and Emotional Wellbeing subscales, suggesting that distress worsens with worsening quality of life. Median time to complete the DT was 4 minutes, and only 1/285 participants found it objectionable.

Study 2 We compared DT scores of patients on haemodialysis with DT scores of patients with CKD4/5. Haemodialysis patients had significantly higher DT scores than CKD4/5 patients, even

following adjustment for age, gender and comorbidities (median DT score 4 for haemodialysis patients and 2 for CKD4/5 patients, $p < 0.001$). Younger age, female gender and previous diagnosis of depression were also associated with higher levels of distress.

Study 3 We obtained records for 316 CKD4/5 patients aged <70 with ≥3 DTs and KPSs in their patient record. 23 started haemodialysis during the study period. Linear regression was used to analyse DT score, KPS and other factors of interest at baseline. Multi-level regression was used to analyse changes in DT and KPS score over time. Visual Graphical Analysis (VGA) was used to assess the trajectories of patients who started dialysis in the study period.

For each 10% loss of functional performance on the KPS, DT score fell by 0.47 ($p<0.001$). The relationship between change in DT scores over time and factors such as gender, eGFR and age, was not statistically significant. We identified four common trajectories of distress around the time of initiation of dialysis. For a minority of participants their DT scores were unaffected by starting dialysis. The majority however saw a rise in their DT scores around the time of start on haemodialysis. For some participants this returned to pre-dialysis distress levels within six months, but for others their distress levels remained high.

Study 4 Using an interpretative phenomenology approach, we interviewed participants about their experiences of distress. Distress appeared to be a near-universal response to the transition onto dialysis, and a broad range of definitions of distress were used by our participants. In particular, delays and lack of individual care led to feelings of alienation of patients from the dialysis team.

Discussion Distress is common in renal patients, and haemodialysis patients appear to experience higher levels of distress than CKD4/5 patients, even following adjustment for other factors. Time of initiation of dialysis seems to be a time of particular distress, and resources should be focused on easing this transition. Individualised care is particularly welcomed by patients.

It would seem that the word “distress” does not unambiguously refer to any one concept, experience, or phenomenon, but rather is a cluster of related terms, with meaning generated

idiosyncratically by each individual. The advantage of the Distress Thermometer is that it is designed to work with whatever definition of distress each patient deploys, without challenging them on that definition.

2 Acknowledgements

Many thanks to my supervisor Aine for her unstinting support and guidance. To Dave Wright for helping with the EPR database queries – you really went above and beyond. To Joe Low, Victoria Vickerstaff and Dorothea Nitsch for their advice on the study design and implementation.

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Thanks to all the patients who very generously gave their time, in particular the participants in the interview study who provided such illuminating insights.

And finally to my husband Mattie and son Sasha – Mattie for the support and endless discussions about floating signifiers, and Sasha for the endless distractions.

3 Table of Contents

3.1.1 **List of tables**

3.1.2 **List of figures**

3.1.3 **Abbreviations used in this thesis**

AMT	Folstein Abbreviated Mental Test
ADL	Activity of Daily Living
BDI-II	Beck Depression Index II
CCI	Charlson Co-morbidity Index
CFN	Centre for Nephrology
CKD	Chronic Kidney Disease
CM / MCM	Conservative Management / Maximal Conservative Management
DT	Distress Thermometer
eGFR	Estimated Glomerular Filtration Rate
ERPF	Effective renal plasma flow
ESRF	End-Stage Renal Failure
GP	General Practitioner (primary care physician)
HADS	Hospital Anxiety and Depression Scale
HCP	Healthcare professional
HD	Haemodialysis
IADL	Instrumental Activity of Daily Living

ICC	Intra-class Correlation Coefficient
KPS	Karnofsky Performance Scale
LCC	Low Clearance Clinic
MoCA	Montreal Cognitive Assessment tool
MDRD equation	Modification of Diet in Renal Disease equation
MMSE	Mini-Mental State Examination
MSAS-SF	Memorial Symptom Assessment Scale (Short Form)
NHS	National Health Service
PD	Peritoneal Dialysis
PREM	Patient-Reported Experience Measure
PROM	Patient-Reported Outcome Measure
RFH	Royal Free Hospital
RRT	Renal Replacement Therapy
SF-36	Short Form (36) Health Questionnaire
UKRR	UK Renal Registry
VGA	Visual Graphical Analysis

4 Background

4.1 The Ageing Renal Patient

In the 1970s and 80s the lack of dialysis provision in the UK was a national scandal. Less than 25% of patients referred for dialysis in the UK were accepted onto a programme (less than half the rate of Sweden), and this was strongly correlated with the distance the patient lived from the nearest renal unit (a true postcode lottery)[1-4]. To combat this shortage, there was an expansion in the number of renal units in the UK towards the end of the 1980s, and the development of the "hub and spoke" satellite dialysis units that are common today[5-8].

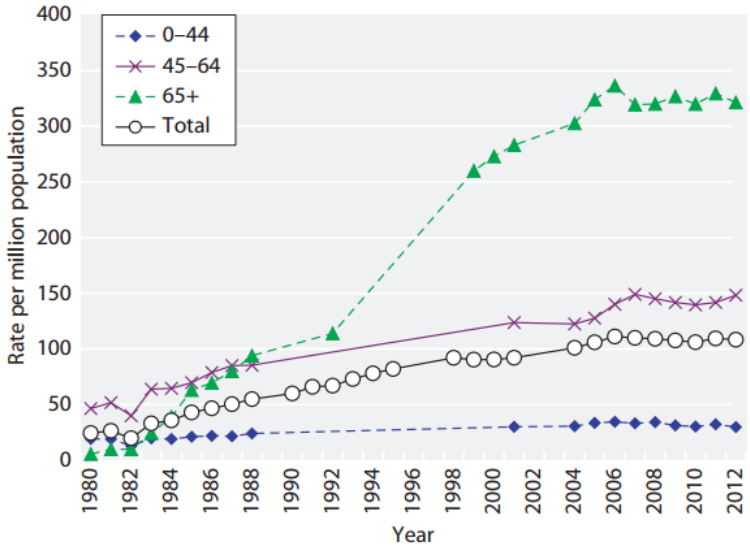


Figure 4.1 RRT incidence rates 1980-2012, UK renal registry 16th annual report, 2013

There has also been a significant expansion in the number of frail older patients diagnosed with advanced CKD over the past thirty years[9]. Indeed, the burden of CKD disproportionately affects older patients. Despite this, the majority of older patients die *with* CKD (due to other comorbidities), not *from* it[10-14].

These elderly patients have high levels of co-morbidity, and as a consequence the face of renal medicine is changing – there is an increasing need to focus on traditionally geriatric areas of expertise such as falls prevention and rehabilitation, and shift in focus onto improving patient well-being rather than longevity. This will involve guiding patients towards treatment options which will maintain their independence and quality of life.

It has become clear that dialysis is not the best option for everyone. The concept of "Maximal Conservative Management" was introduced in some units around 15 years ago (notably, the Royal Free Hospital was one of the first)[15,16] and is now an established treatment choice in the majority of renal units in the UK. It provides symptom control, non-dialytic correction of electrolyte and fluid imbalances, anaemia management, and end of life care. The emphasis is on maintaining quality of life for the patient and their families (described as "rational care, not rationing care"[17]).

Unfortunately it is difficult for nephrologists to advise patients whether to choose dialysis or conservative management. There is not currently enough evidence to allow accurate prediction of who will do well on dialysis and who will not. Some older patients do extremely well on dialysis. For others, particularly those patients with multiple co-morbidities or at the extremes of old age, survival is similar on conservative management as it would have been on dialysis[17-19]. It is also not clear which patients will feel better on dialysis and who will not. The evidence to date suggests that patient's self-reported quality of life may worsen on dialysis while those patients who have chosen conservative management do not see a significant decline[17]. Currently some patients who would probably have an increased survival on dialysis choose to sacrifice longevity for a better quality of life[20]. For most patients this remains a very personal decision.

Over the last ten years the research picture has changed considerably. Recent small scale and qualitative studies have changed the perception of older patients' experience of end-stage kidney disease and have legitimised conservative management as the fourth option for ESRF along with haemodialysis, peritoneal dialysis and transplantation. The challenges now faced include expanding

the evidence base in this area with larger epidemiological studies. Many of these patients have multiple comorbidities and are housebound, and many die before they reach end-stage renal failure, so any longitudinal studies which undertake to follow patients from CKD to ESRF must recruit large numbers of patients in order to have sufficient patients starting dialysis. Many of the tools used in this area are unwieldy and difficult for frail older patients, some of whom have cognitive or visual impairments, to complete.

4.2 Older patients with Chronic Kidney Disease in the UK

CKD disproportionately affects older patients (Figure 4.2, Figure 4.3)[9,10,21,22]. Since 2006 UK primary care providers have maintained CKD disease registers as part of Quality and Outcomes Framework (QOF)[23], and more patients are now diagnosed and referred to nephrology clinics from primary care[24]. There is debate about whether this higher incidence of reduced eGFR in older patients represents normal ageing or a disease process[25]. There has been shown to be an age-related reduction in effective renal plasma flow (ERPF) and increase in renovascular resistance in even healthy older patients[26]. These changes in renal haemodynamic autoregulation lead to an increased risk for acute kidney injury (AKI) from relatively small insults. Many older patients also develop a reduced glomerular filtration rate and have fewer nephrons than younger patients, although this may be related to underlying macrovascular disease as up to a third of normotensive older patients maintain a normal GFR[27,28].

In addition, the most common method of diagnosing CKD in the UK is by estimating GFR from serum creatinine. There are potential problems with this, as serum creatinine is related to muscle mass which may decline in older patients leading to an overestimation of glomerular filtration rate. The MDRD equation is the most commonly used equation in NHS labs. The newer CKD-Epi equation[29], although currently less commonly used, is thought to be more accurate at higher glomerular filtration rates. However both equations have recently been validated in older patients[30]. Newer

biomarkers (such as cystatin C) which are not related to muscle mass may give a more accurate estimation of GFR in sarcopenic patients, but are expensive, not currently widely available, and may have their own drawbacks (for example, cystatin C may be elevated in inflammation[31] and may also be affected by factors such as smoking history, gender and age independent of kidney function[32]).

Finally, a large proportion of CKD in the UK is associated with hypertensive/renovascular disease, diabetic nephropathy, or obstructive uropathy (due to prostatic disease or bladder dysfunction), all of which disproportionately affect older patients. The most recent UK renal registry report found that the median age of incident RRT patients was 64.6yrs[9]. A still greater number of older patients with CKD will never progress to end-stage renal failure[10] (Figure 4.4) but many of these will still have the symptoms and decreased life expectancy associated with CKD.

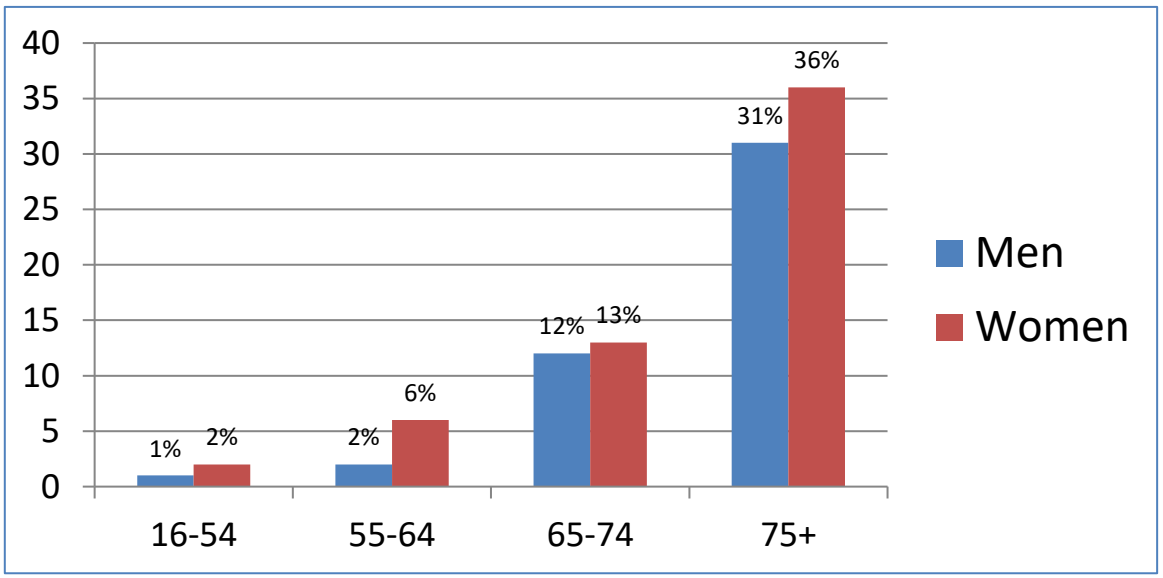


Figure 4.2 Incidence of CKD 1-5 in the UK (Roderick et al, 2011)[22]

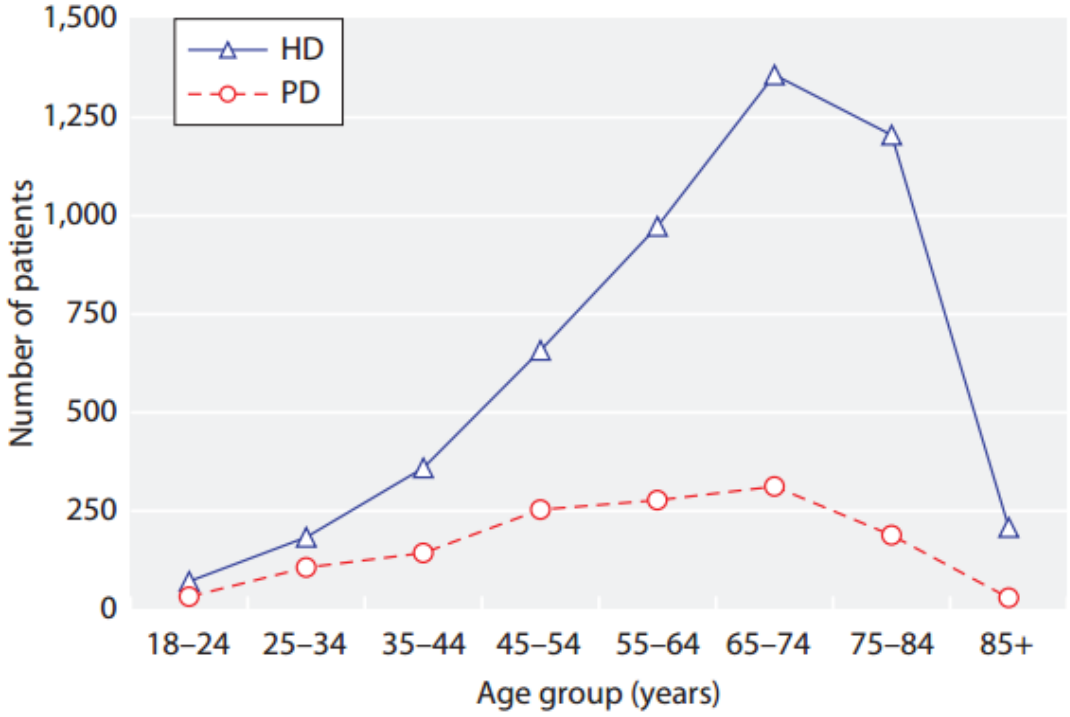


Figure 4.3 Number of incident dialysis patients in 2012, by age group and initial dialysis modality (UK renal registry 16th annual report, 2013)[9]

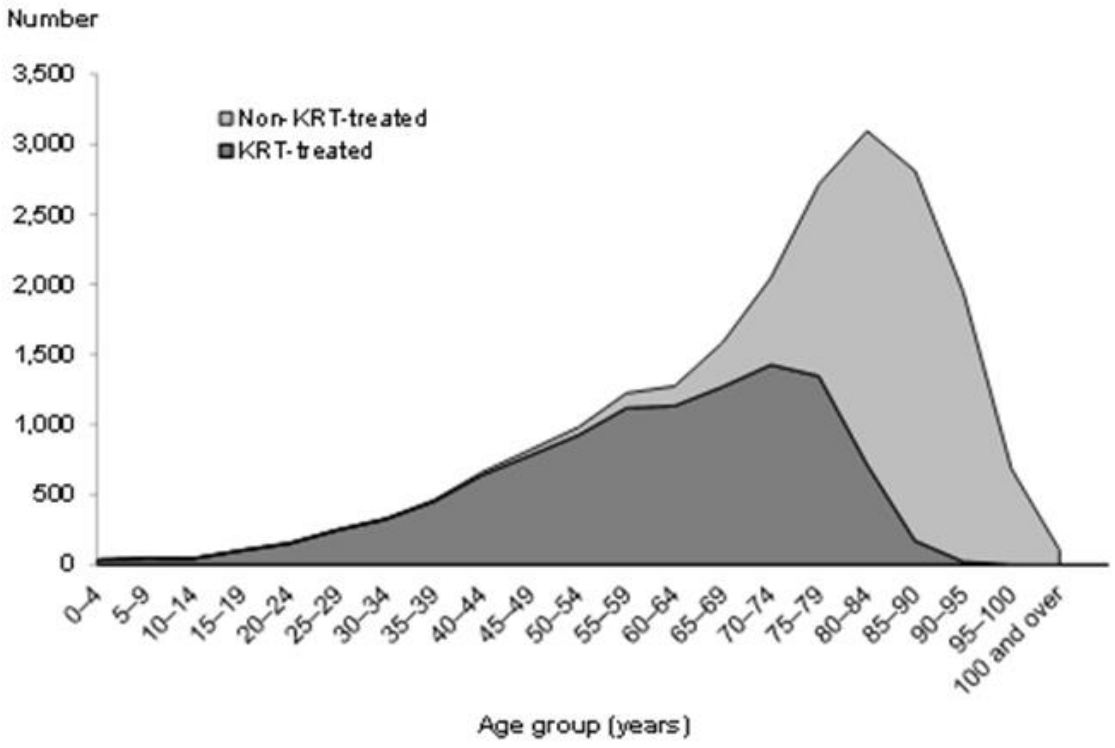


Figure 4.4 Proportion of patients with CKD V receiving RRT compared with those who do not, by age group (Moon et al, ANZDATA registry report, 2011)[10]

4.3 Survival in older patients with CKD

Survival in older renal patients is known to be poor. UK renal registry data shows that new starters on dialysis who are aged over 75 have a 30% mortality rate within the first year, and more than half will be dead within two years (Figure 4.5)[9]. Five year survival is less than 20%, worse than many cancers (Figure 4.6)[33]. Many nephrologists may find it difficult to be explicit with patients about this.

It could be argued that the excess mortality in older incident dialysis patients is in part due to older patients with multi-organ failure being started on dialysis inappropriately, for example because they are too frail to be accepted by the intensive care unit. However when patients who died within 90 days of starting dialysis are excluded, the survival rate for patients aged 65-74 only improves by 5%, and the survival rate for patients aged 85 and older does not improve at all (Figure 4.7).

The UK Renal Registry does not currently collect data on patients who choose conservative management or who have stable CKD5, however a number of smaller studies have compared outcomes for these patients[6,17-19,34-39]. Taken as a whole, patients who choose to dialyse do generally live longer that those who choose MCM, although it does vary quite significantly from study to study, depending on definition of MCM (Figure 4.8). However, they also spend much more time in hospital (including outpatient dialysis appointments) (Figure 4.9)[18] and frequently report that they are so exhausted after a dialysis session that they cannot even manage to prepare a meal.[40,41]

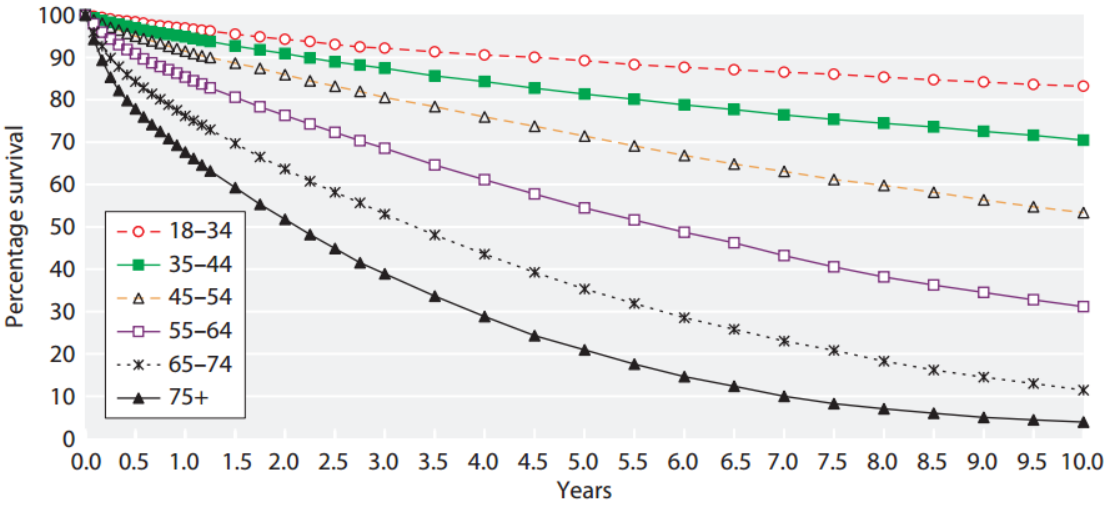


Figure 4.5 Survival of incident patients (unadjusted) 1997-2011 cohort (without censoring at transplantation), UK renal registry 16th annual report 2013[9]

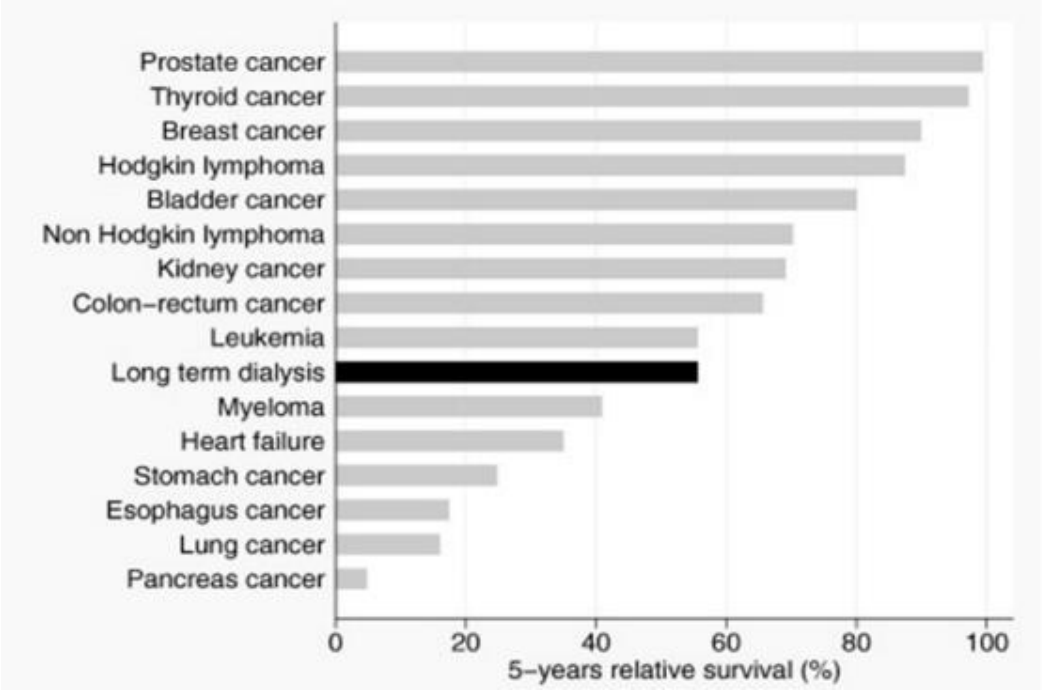


Figure 4.6 Relative 5 year survival of dialysis patients compared with cancer patients. Nordio et al, AJKD 2009[33]

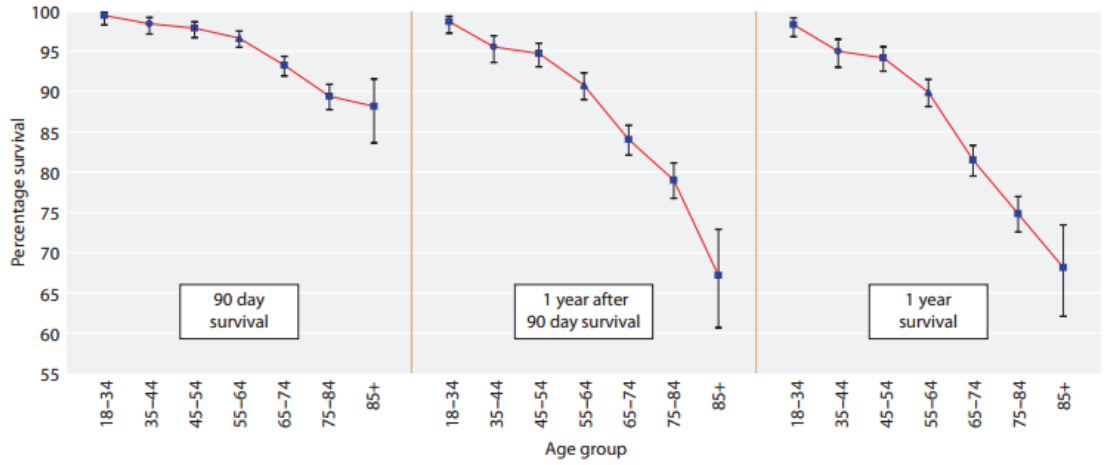


Figure 4.7 Unadjusted survival of incident RRT patients by age group, 2011 cohort. UK renal registry 16th annual report 2013[9]

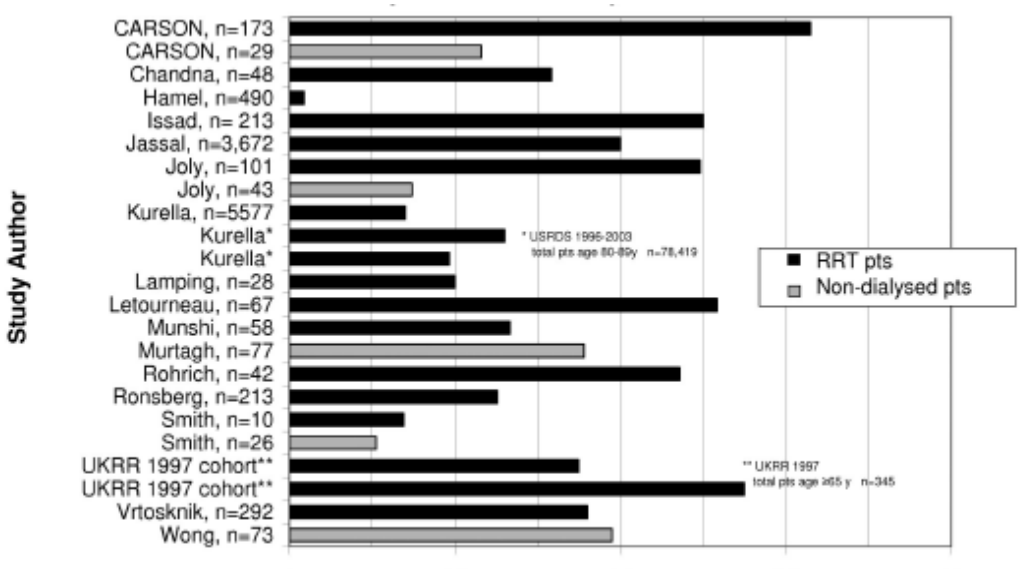


Figure 4.8 Review of median survival of elderly ESRD patients reported in the literature. Carson et al, CJASN 2009[18]

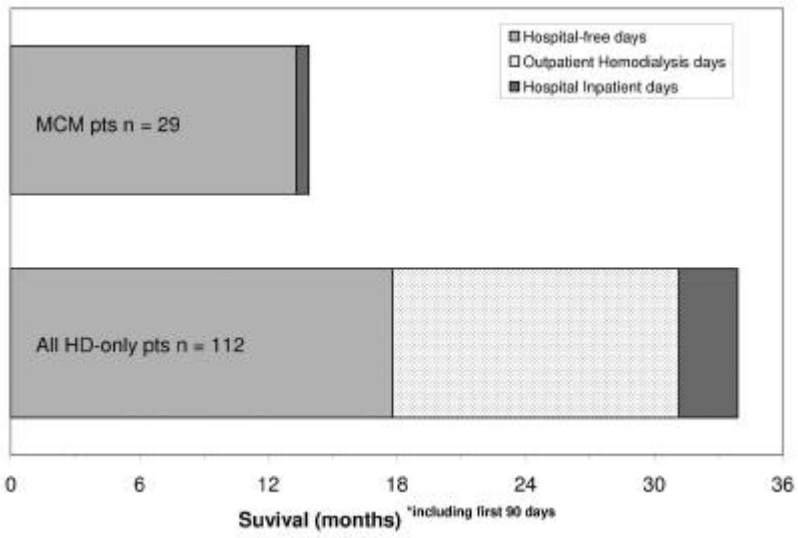


Figure 4.9 Relative survival of HD patients and MCM patients. Carson et al, CJASN 2009[18]

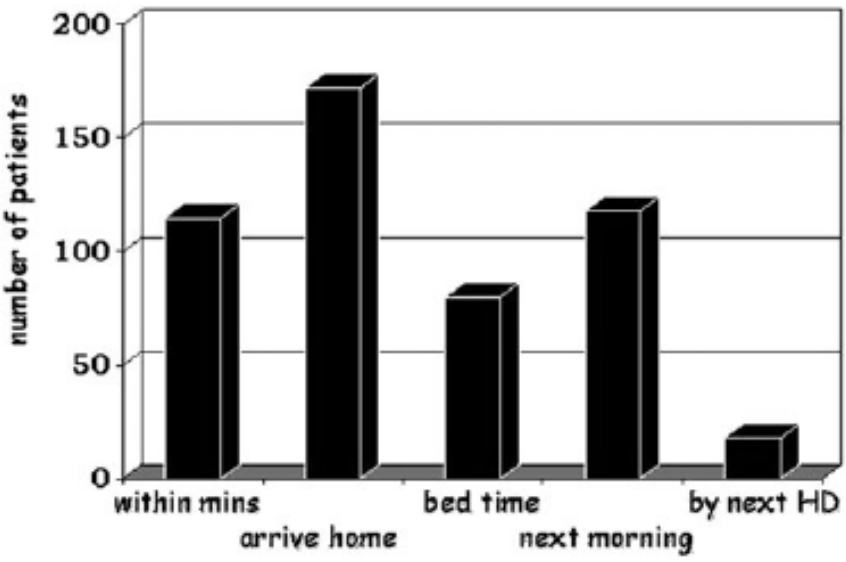


Figure 4.10 Time to recovery following dialysis sessions. Source: Caplin et al, NDT 2011[41]

When we consider those patients with high levels of comorbidity however, the picture is somewhat bleaker. As Murtagh et al showed, the survival benefit of dialysis for patients aged >75 disappears in those patients with high comorbidity[19] (defined as Davies comorbidity score >2).

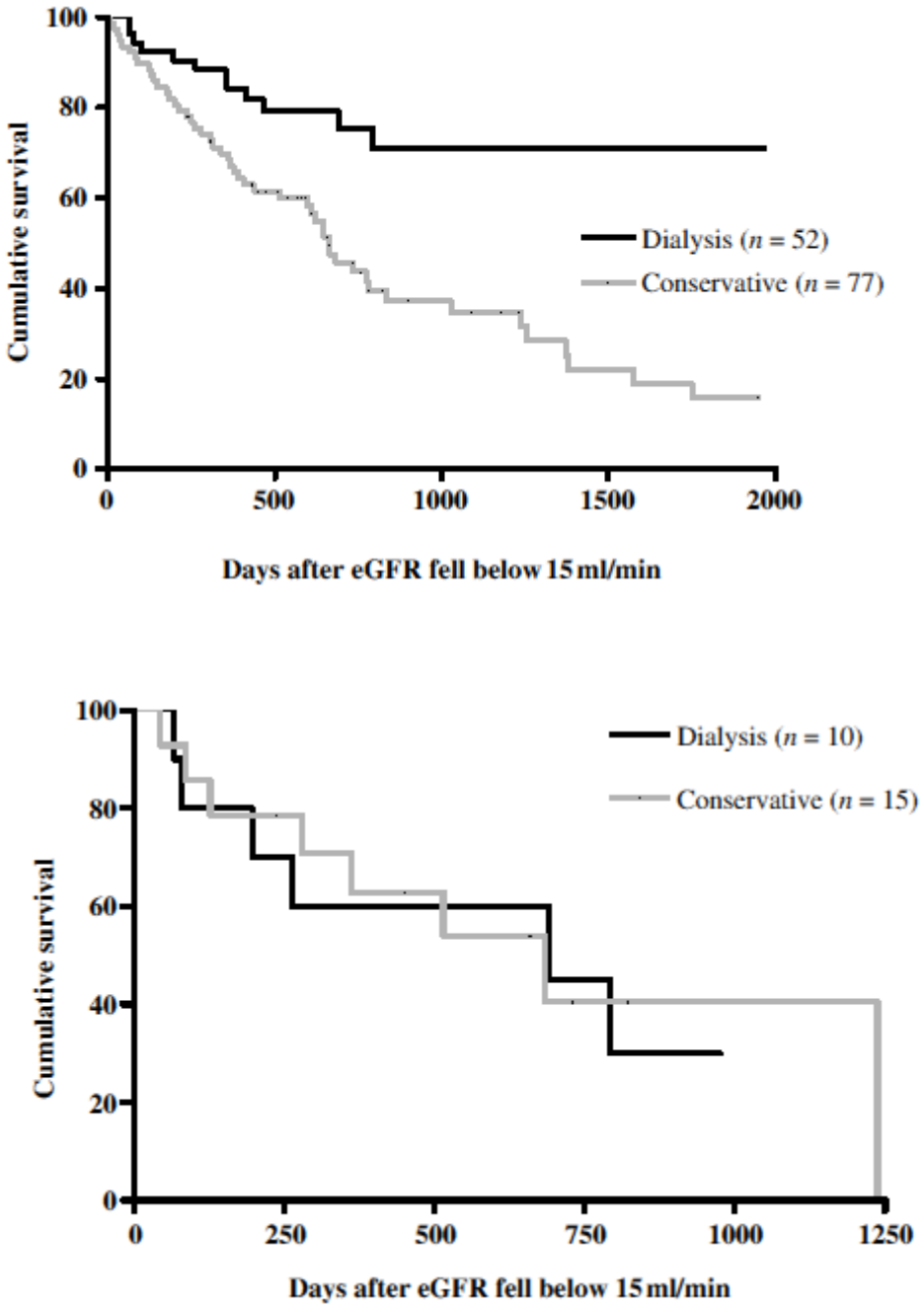


Figure 4.11 Relative survival of patients on MCM and HD pathways, stratified by low comorbidity (top graph) and high comorbidity (bottom graph). Source: Murtagh et al, NDT 2007[19]

This is consistent with other studies, such as Davies[42], and the Rein renal registry[43], both of whom showed that survival in ESRF is greatly reduced in the presence of either diabetes or cardiovascular disease. Cohen[44] showed worse survival in haemodialysis patients with low albumin, peripheral vascular disease, dementia, and a negative answer to the "surprise question" ("Would you be surprised if your patient died in the next six months?"). Interestingly, the "surprise question" alone has high discriminating power when asked of nephrologists and senior dialysis nurses[44-46]. This suggests that failing dialysis patients are actually well-recognised within the dialysis unit. The concern is that in many units, this recognition does not automatically prompt intervention and is not discussed with the patient or their family[47-49]. Regular screening for failing dialysis patients, the use of Advance Care Planning (ACP) tools, and the creation of "cause for concern" registers in some units, aim to address these issues[50-60].

Survival calculators now exist which can improve the advice we give to older patients about their life expectancy on dialysis. For example, the Cohen survival calculator (based on the CJASN paper above[44]) is available as a web-based calculator (http://touchcalc.com/calculators/sq) and a smartphone app. However these predictions must always be individualised for each patient, and there is a margin of uncertainty in any prediction.

4.4 Comorbidity and quality of life in older CKD and dialysis patients

4.4.1 Comorbidity

Older renal patients have been shown to have high levels of comorbidity[44,61-63] and excess mortality from both cardiovascular and cerebrovascular disease as well as cancer[9,33,43,64-71]. A forty year old patient on dialysis has the same annual cardiovascular mortality rate as an eighty year old in the general population and 80% of US haemodialysis patients have some form of cardiac disease (including coronary artery disease, valvular disease, and heart failure)[72].

There are several potential reasons for this. Firstly, the cardiovascular disease may predate or even have caused the renal disease (in the case of cholesterol embolisation following PCI, or severe congestive cardiac failure). Both diseases may be caused by the same underlying condition (for example in patients with diabetic nephropathy, diabetes may be the cause of both the cardiovascular disease and the renal disease). It is possible that renal insufficiency is in itself an independent risk factor for cardiovascular disease. CKD may also simply be a surrogate marker for the presence and severity of an underlying pathogenic atherosclerotic process[71].

There is an association between vitamin D deficiency and renal mineral bone disease, and increased cardiovascular risk[73,74]. It is suggested that altered vitamin D metabolism and secondary hyperparathyroidism may be independent risk factors for cardiovascular disease, by activating the renin-angiotensin system and by increasing vascular calcification.

When established cardiovascular disease has developed, patients with ESRF do less well than patients with normal renal function[75]. Partly this is because acute coronary events are recognised less promptly in dialysis patients (who are more likely to present atypically[75,76], with pulmonary oedema but no chest pain, and less likely to present with dynamic ECG changes). Anecdotally there is widespread confusion about the role of troponin assays in renal patients with suspected acute coronary syndrome, even amongst cardiologists. These patients are also offered less treatment than patients in the general population (less likely to be offered lower PCI/CABG, perhaps due to concerns

about giving contrast, or concerns about poorer surgical outcomes)[72,76]. Randomised controlled trials (RCTs) often specifically exclude renal patients, and so management is often based on "common sense", or by treating renal patients exactly the same as patients with normal renal function[77].

Unfortunately, there have been several instances where RCTs were later carried out and the evidence did not in fact support either of those approaches[72]. The phrase "reverse epidemiology"[65,70,78] is used to describe the fact that conventional risk factors of cardiovascular disease and mortality in the general population such as body mass, serum cholesterol, and blood pressure are also found to relate to outcome in maintenance dialysis patients, but in the inverse direction. For example being overweight is associated with an increased cardiovascular mortality risk in the general population, but is associated with a reduced annual cardiovascular mortality risk in haemodialysis patients[65,70].

The high rate of death from cancer is also likely to be multifactorial – some patients will have a history of immunosuppression either due to their underlying renal disease or previous renal transplants, giving a higher incidence of cancer overall. Many chemotherapeutic drugs cannot be given to patients with renal impairment due to the risk of toxicity[33], so patients do not have access to the full range of treatment options which are available to those with normal renal function. Renal patients may also have less functional reserve[79], and be more likely to develop sepsis (preventing further cycles of chemotherapy).

4.4.2 **Symptoms**

Renal patients report high symptom burden, whether they are CKD patients[80], dialysis patients[81], or transplant patients[82]. Indeed, it has been noted that "patients with stage 5 CKD have considerable symptom control needs, similar to advanced cancer populations"[80].

Individual symptoms may fluctuate day by day (Dineen, unpublished data). Fatigue is a major symptom, along with itch and loss of appetite[40,49,80,81,83-92]. Again, there are numerous reasons for

this. Uraemia itself causes many symptoms such as fatigue, itch and loss of appetite. Renal anaemia may also contribute to loss of energy, shortness of breath, and to other symptoms such as angina.

Patients report high levels of pain[93-96], but this often goes untreated. This may partly be due to reluctance in medical professionals to prescribe painkillers. NSAIDs are nephrotoxic (although this is less of a concern in patients who no longer have any residual renal function) and may cause GI bleeding (a significant problem in renal patients, who are already at increased bleeding risk due to platelet dysfunction, and who may already be on other anti-platelet drugs as secondary prevention in macrovascular disease). Opioid painkillers and other agents such as gabapentin may accumulate in severe renal failure, although these can usually be given safely if the dose is reduced or dosing interval is increased. Finally, renal patients may not be offered interventions for their pain (knee replacement, cardiac surgery) due to their increased risk of complications.

There is also a relationship between symptom burden and both depression and poor functional status[81,89,91-95], which will be discussed further in subsequent sections.

4.4.3 **Performance status**

CKD and dialysis patients have high rates of dependency. In the US, 11% of new-starters on haemodialysis aged over 70 are in a nursing home[97], and these patients have very poor outcomes[98-102].

Kurella Tamura et al[101] found that physical function declined rapidly in the three months before initiation of haemodialysis, which might be expected due to increasing uraemia. However, contrary to expectation physical function did not appear to recover following initiation of dialysis, and patients remained significantly functionally impaired. Jassal et al[103] found that 30% of new starters on dialysis became more functionally dependent within the first six months of being on haemodialysis, including those patients who had previously lived independently. Although functional status did not worsen after the first six months, it did not improve either. In contrast, Murtagh[104]

found that patients managed conservatively maintained functional status until the last month of life. There is the possibility of lead-time bias here – patients were included in the study when eGFR was <15mls/min (ie long before dialysis would usually be initiated) and eGFR at point of death was not recorded, so it is quite possible that "last month of life" is equivalent to (or even earlier than) "time at which patient would have started dialysis if they had not been managed conservatively".

A later study by Cook and Jassal[105] found that in a cohort of 168 prevalent haemodialysis patients aged over 65 years, only 5% were independent in all ADLs and IADLs, and 53% were dependent in at least one of the six basic ADLs. Almost half were unable to wash without assistance. Only a quarter could rise from a chair without using their arms, and less than a third had normal balance. Over 30% had fallen at least once in the previous year. Functional status is somewhat better in peritoneal dialysis patients[106], but this may be due to patient selection (if assisted PD is not available, only patients with relatively good functional status will be offered PD).

There are several possible reasons for the high levels of dependency seen in CKD patients. Firstly, as previously discussed, these patients have high rates of comorbidity[42,107-110] including high rates of diabetes and macrovascular disease, which may cause physical dependency. Secondly, chronic kidney disease itself often causes metabolic disturbances associated with fatigue and weakness, such as acidaemia, anaemia, peripheral oedema and pulmonary oedema.

There have been several suggestions about how to reverse this functional decline. Correction of acidaemia has been associated with improved muscle strength[111]. However it is not yet known whether this translates to a meaningful improvement in functional status – more studies need to be carried out in this area. Correction of anaemia has not been shown to reverse functional decline[112,113]. The effectiveness of rehabilitation is hotly debated – some researchers have found it to be effective[114-118], while others have not found any benefit[119]. This is probably due to differences in patient selection[120-124], for example patients with cognitive impairment are much less likely to achieve rehabilitation goals.

4.4.4 **Frailty**

Frailty, defined by Clegg et al as a cumulative decline in multiple physiological systems and impairment of homeostasis leading to increased vulnerability to external stressors[125], is a key area of great interest in current geriatric research, and is seen as one of the "Geriatric Giants" (along with falls, dementia and incontinence). It is a concept which has long been widely understood as a marker of decreased physiological reserve and increased mortality by clinicians. However, although most geriatricians "would know it if they saw it", there is still no firm consensus on the use of tools to diagnose or screen for it.

There are two main models of frailty – the Rockwood Frailty Index, which views frailty as an accumulation of deficits, with patients moving along a continuum from non-frail to frail[126], and the Fried Frailty Phenotype, which sees frailty as a syndrome which is either present or absent[127], based on presence of three or more of the following criteria: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity. In both models, this cumulative decline depletes homoeostatic reserves until minor stressor events trigger disproportionate changes in health status (for example, a minor urinary tract infection may lead to delirium and bedfastness in a frail patient, while the same illness would have minimal effect on a robust patient of the same age).

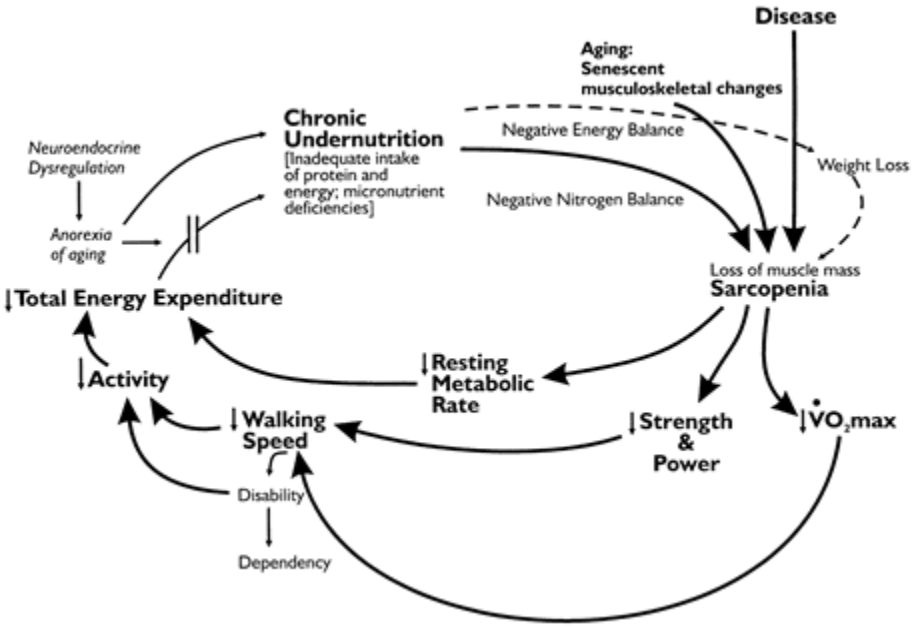


Figure 4.12 The cycle of frailty. *Principles of Geriatric Medicine and Gerontology,* 4th Ed. McGraw-Hill 1999[128].

A high proportion of renal patients are frail. Indeed, some studies have shown that over 78% of dialysis patients aged over 70 would meet the Fried frailty criteria[79,129,130] , compared with 6.9% of Fried's original cohort of older patients with normal renal function[131]. There are a number of possible reasons for the extremely high proportion of frail dialysis patients - in a later study, Fried found an association between protein-energy wasting and both impaired renal function and chronic inflammation[132]. This may be exacerbated by poor intake due to uraemia and dietary restrictions. High levels of comorbidities, frequent infections and regular hospital admissions in this population will also predispose to frailty. This has a number of implications for nephrologists – should we screen for frailty, if it is so prevalent? And how should we intervene when we find it?[133]

The most evidence-based intervention for frailty is the comprehensive geriatric assessment (CGA), defined as "a multidimensional interdisciplinary diagnostic process focused on determining a frail older person's medical, psychological and functional capability in order to develop a coordinated and integrated plan for treatment and long term follow up"[134]. The resources are not currently in place

to allow a comprehensive geriatric assessment for 80% of our prevalent dialysis patients, but pilot studies by Jassal and others which offered CGA to older new starters on dialysis have shown promising early results[116,118,135]. Another option might be the wider use of "Cause for Concern" screening tools to identify the failing dialysis patient and to intervene early.

4.4.5 **Falls/fractures**

Older dialysis patients frequently fall[136-138], when they do fall they are at increased risk of fractures[139-143], and they are more likely to have poor outcomes than similar-aged patients with normal renal function[143-146]. Cook and Jassal found that over 30% of dialysis patients aged over 65 had fallen at least once in the previous year, and only 20% of patients had normal timed functional mobility scores[105]. Post-dialysis hypotension, underlying cerebrovascular and cardiovascular disease, polypharmacy, autonomic dysfunction and peripheral neuropathy (due to co-existing diabetes and deposition of B2 microglobulin) are just some of the potential causes of these falls. There is an association between vitamin D deficiency, somatic muscular weakness and falls risk in both renal patients and the general population[74,137,147,148]. Many patients have amputations[149-152]. Many patients also have visual[153] or cognitive problems[154], and trying to climb off and onto the bed for dialysis and then to negotiate a busy, noisy dialysis unit can be a disorientating experience for many older patients. In addition, patients with cognitive problems have higher rates of falls when their attention is distracted[80,81], and dialysis units are generally rather distracting places.

Awareness of some of these problems can lead to risk reduction[143] – for example, regular medication reviews, omitting antihypertensives on the morning of dialysis to prevent hypotension, removing trip hazards in the dialysis unit and offering assistance with transfers, and early screening and referral to physiotherapy or occupational therapy for walking aids and grab rails. Simple screening tools such as the sit-to-stand test and the timed up-and-go are effective at predicting falls risk[155], and can easily be carried out in clinic or on the dialysis unit.

4.4.6 Depression and Quality of life

Depression is widespread in renal patients – there is wide inter-study variation depending on the diagnostic criteria used, but it is generally accepted that between 20-30% of dialysis patients are depressed[156]. This should not be surprising, as studies in non-renal illness have found correspondingly high levels of depression in similarly functionally dependent patients[157]. Depression in dialysis patients is associated with higher morbidity and mortality[156,158-165], higher functional dependence[83,166,167], and worse quality of life[83,166]. Depressed renal patients are more likely to be malnourished[168], more likely to be non-adherent to dietary and fluid restrictions[169-174], and more likely to complain of somatic symptoms[40,83,91,170,175-177], although the direction of causality is not clear. They are also more likely to withdraw from dialysis[156,178], although it may be that both the depression and withdrawal from dialysis are caused by disease severity, rather than that patients withdraw solely due to depression. Most renal units in the UK now have a renal psychologist or counselling service, however depression remains under-recognised[179]. This may in part be patient-led – Wuerth found that many patients refused evaluation for depression and were non-adherent to antidepressant medication therapy, perhaps due to the stigma which still remains around mental illness[180].

Unsurprisingly, given the high levels of functional dependency, depression and symptom burden in many renal patients, quality of life has been found to be generally poor[83,96,181-185], particularly for those patients on dialysis. Da Silva Gane[17] found that quality of life worsens after dialysis start, particularly in haemodialysis patients. In contrast, patients managed conservatively maintained their quality of life. Interestingly, Moser[186] found that older patients were likely to have better self-reported quality of life than younger patients despite having more functional impairment, due to their lower expectations. This is supported by other studies suggesting that good family and social support, socioeconomic factors, an external locus of control, good psychological coping strategies

and higher levels of disease acceptance were all associated with higher self-reported health-related quality of life, while disease intrusiveness was associated with lower quality of life[187-198].

Cognitive function

An estimated 30-70% of haemodialysis patients have been shown to have some degree of cognitive impairment[154,199-203], and incidence of new cognitive impairment has been associated with both severity of chronic kidney disease[200,204,205] and with both rate of decline of renal function and albuminuria[206]. This is probably due to a combination of comorbidity (presence of diabetes, vascular disease and hypertension are all independent risk factors[207,208]) and factors unique to chronic kidney disease, such as the presence of uraemia.

Cognitive function is worse during dialysis sessions[209], presumably due to reduced cerebral perfusion, and best either just before or the day after a dialysis session. It does not seem to improve with more frequent haemodialysis[210], and there is conflicting evidence regarding improvement following transplantation[211-213], suggesting that some of this damage may be permanent.

Visuospatial and executive functions are disproportionately affected in these patients[207,214,215], and NHANES III found slower learning speeds and impaired visual concentration even in otherwise healthy, younger CKD patients (aged 20-59), compared with standardised populations[216]. This has obvious implications for pre-dialysis counselling and patient education programmes, as well as with treatment compliance. Importantly, these deficits may not be immediately obvious to clinicians in the way that loss of short-term memory or orientation might be, and will also not be detected using short screening tools such as the Abbreviated Mental Test (AMT), which is widely used to screen for dementia in patients acutely admitted to NHS hospitals.

The presence of cognitive impairment has been linked with an increased risk of hospitalisation[217] and death[202] in this population, and there are probably several reasons for this. Firstly, the presence of comorbidities such as diabetes and vascular disease will predispose patients to both cognitive impairment and higher rates of hospitalisation and death. However difficulties in taking medications or following dietary or fluid restrictions due to impaired executive function may also play a role.

Lastly, it is important to understand that for many older patients, there is an overlap between depression and dementia[218-220]. Depression may give rise to pseudo-dementia, where low mood causes poor motivation and the appearance of cognitive impairment. Equally, many patients with dementia do become depressed. It can be very difficult to distinguish between the two, even with very careful history-taking. In patients who do exhibit signs of depression, cognitive function should be re-assessed following treatment of the depression before a diagnosis of dementia is made.

4.5 Choosing the right modality and Advance Care Planning

Traditionally, renal replacement therapy has always been seen as the logical end-point for CKD, and since the late 1990s the Low Clearance Clinic model[221-226] has been used to provide pre-dialysis patients with information about the renal replacement therapy options available to them. Conservative (non-dialytic) management was not seen as part of the nephrologist's remit, and patients who were not suitable for (or not willing to have) dialysis were discharged back to the community (or indeed never referred in the first place)[16,62,227]. This meant that these patients missed out on specialist symptom management (such as anaemia management, correction of acidosis, and specialist dietary advice).

Over the past 10-15yrs, evidence that high-risk patients (those who are older, with multiple co-morbidities, dementia or vascular disease) have very poor survival[9,33,44,108,130,228,229], and survive as long (or maybe even longer) without dialysis[17,19,35,230], has changed this picture. Conservative

management is now widely seen as a valid alternative to dialysis in renal centres in the UK[16,34,38,231], providing specialist renal palliative care (there are often links with local community palliative care services[232]).

The challenge is now to ensure that the information that we give to older patients is accurate and appropriate to them. Davison[233-236] demonstrated that patients do actually want to know about their prognosis, and need to be able to plan ahead. Our preconceptions about patients' quality of life may also be inaccurate or paternalistic - Rachel Morton[237,238] found that patients and carers prioritised convenience and dialysis-free days, and indeed patients would be willing to give up 23 months of life in order to travel more. These preferences should be discussed with patients while they are well, so that we can focus our care on the areas that matter most to them as part of the Advance Care Planning process[51,222,234,239,240].

Equally important, when the leading cause of death among dialysis patients in the US is withdrawal from dialysis[130], we need to start conversations about future options with failing dialysis patients early. The Surprise Question ("Would you be surprised if this patient died in the next 6 or 12 months?"), particularly when asked of senior clinical staff in the dialysis unit, is robust at identifying short-term mortality risk in these patients[44-46,241]. Frailty screening has also been discussed[129,228,242,243]. The tool used to identify these patients is probably less important than the fact that discussions are taking place and that the patient has the opportunity to make their wishes known, even if that does not lead to a formal Advance Care Plan [51-53,56,57,59,60,244].

4.6 Patient reported outcome measures and experience measures in CKD

Given that hard outcomes such as survival seem to be so similar between many dialysis and conservatively-managed patients, many researchers have turned their attention to more subjective outcomes such as quality of life, pain, and symptoms. Patient-reported outcome measures are

widely used both clinically and in health-related quality of life research, and provide an insight into the way patients perceive their own health and the impact that a treatment or disease has on their life.

There is also a new focus in the NHS on "improving the areas that matter most to patients" in the light of recent inquiries into the standard of NHS care. The Government White Paper, "Equity and excellence: Liberating the NHS"[245] envisaged an increase in the scope and coverage of Patient-reported outcome measures (PROMs):

"Information generated by patients themselves will be critical to this process, and will include much wider use of effective tools like Patient Reported Outcome Measures (PROMs), patient experience data, and real-time feedback. At present, PROMs, other outcome measures, patient experience surveys and national clinical audit are not used widely enough. We will expand their validity, collection and use. The Department will extend national clinical audit to support clinicians across a much wider range of treatments and conditions, and it will extend PROMs across the NHS wherever practicable."

It is important to distinguish between patient-reported outcome measures (PROMs), which measure outcomes, and patient-reported experience measures (PREMs), which look at the overall patient experience. Patient-reported experience measures have arisen from patient satisfaction surveys and feedback forms, but unlike these tools PREMs focus on what actually happened to the patient rather than their feelings about it. For example, "how long did you wait for transport (in minutes)", rather than "are you satisfied with the amount of time you waited for transport". This both gives a focus for improvement for service managers, and prevents the ceiling effect, where all respondents are "fairly satisfied".

The use of patient-reported experience measures (PREMs) is not novel in the US, where Medicare and Kaiser Permanente facilities among others have used annual reports such as the Hospital

Consumer Assessment of Healthcare Providers and Systems (HCAHPS) to drive service improvement for many years.

At its most basic, this includes the use of the "Friends and Family" test (whether patients or staff would advise their friends and family to be treated at their local hospital). The UK Renal Registry is currently working on adopting some of these measures to assess quality of dialysis care in the UK.

There are many different patient-reported outcome tools available. Some are specifically validated in renal patients, others are used descriptively (often in a wide range of diseases) and there is therefore no gold standard to validate against. I have described the most commonly used self-report tools below, with their main advantages and disadvantages.

4.6.1 **Symptoms**

Several symptoms scores are established for use in renal patients. Probably the most widely-used in the UK are the **Memorial Symptom Assessment Score** (MSAS), and its renal-specific version the MSAS-SF (Renal). The MSAS was designed to be used in a wide range of different patient groups, and is therefore quite broad. It comprises 32 physical and psychological symptoms, assessed by severity, which then gives an overall score and three subscores (physical, psychological, global distress). The **MSAS-SF (Renal)** was developed by Murtagh[80] in 2007. It consists of the 32-item MSAS-SF with seven additional symptoms which have been found to be common in CKD patients: joint and bone pain; muscle cramps; dry skin; muscle soreness; headaches; chest pain and restless legs. This renal-specific score may be more sensitive at detecting symptoms in renal patients, however it is at the cost of being somewhat longer.

The **Edmonton Symptom Assessment System** (ESAS) was validated for both cross-sectional and longitudinal use in renal patients by Davison et al in 2006[87,88]. It was validated against the Kidney Disease Quality of Life short-form scale (KDQOL-SF), which is not itself a measure of symptom

burden (see below). The ESAS is a visual analogue scale assessing the prevalence and severity of 10 symptoms (pain, tiredness, depression, anxiety, drowsiness, nausea, loss of appetite, well-being and shortness of breath, plus "other" of patient's choosing). It has the advantage of being free to use, relatively short (1 page) and broad (combining both somatic and psychological symptoms). Conversely, it is not particularly detailed and may miss less common symptoms.

The **Dialysis Symptom Index**[92] is a 30-point patient-reported symptom assessment score devised specifically to assess symptoms which are common in dialysis patients. Scores >9 are usually seen as significant in a research context. The main drawback it its length, which makes it impractical for frequent use. However it is free to use, very comprehensive, and as it was created using dialysis patient focus groups, it is considered to be particularly well-suited for use in renal patients.

The **Modified Transplant Symptom Occurrence and Symptom Distress Scale**[82] was specifically designed to assess symptoms associated with transplant immunosuppression (as these symptoms may affect adherence). It does not have utility in the general renal population.

4.6.2 Depression

The most common depression screening tools used in renal patients are the **Hospital Anxiety and Depression Scale** (HADS)[246,247], and the **Beck Depression Index II** (BDI-II). Other scales, such as the **Geriatric Depression Scale**, have also been used in renal patients[248-250] but have more limited application (older patients only). All are validated in renal patients[248,249,251].

The HADS, first devised by Zigmond and Snaith in 1983[246], is a 14-item multiple-choice self-report inventory based on how the subject has felt over the past week. Each item is scored 0-3, giving a total score 0-21 for depression, 0-21 for anxiety, and 0-42 overall. This scale was designed to screen for depression and anxiety in hospital patients without being affected by the presence of physical symptoms which may be related to the underlying illness rather than depression. Validated by

several groups for use in renal patients, using psychological interview as gold-standard, a score of 12 is said to represent "caseness" in renal patients[251].

The original BDI was devised in 1961 by Beck. It was extremely novel for its time; patients' verbatim descriptions of symptoms were collated, and these were used to structure a scale which could reflect the intensity or severity symptoms. The BDI was revised in 1996 to reflect the changes in the DSM-IV diagnostic criteria of depression[252]. The BDI-II is a 21-item multiple choice self-report questionnaire; each item is scored 0-3, giving a total score of 0-63. In the general population, the following cut-offs are used: 0–13: minimal depression; 14–19: mild depression; 20–28; moderate depression; and 29–63: severe depression. Higher total scores indicate more severe depressive symptoms. In renal patients, there is no accepted cut off to indicate "caseness", as previous validation studies have demonstrated cut offs between 10-15 depending on the gold standard used[248,251,253]. For the purposed of this project, we used a cut-off of 13 which was obtained from the Loosman study which simultaneously validated both the BDI-II and the HADS in renal patients, so that the cut offs used for both tools were validated against the same gold standard (psychological interview).

The main drawback to the BDI-II is its cost – it is under copyright and must be licensed for use. In addition, as it is based on the APA's DSM IV diagnostic criteria for major depression, it includes somatic symptoms such as sleep and appetite disturbance, which may be due to the underlying renal failure rather than depression per se.

The Geriatric Depression Scale (Short form) is a 15-item self-report assessment to identify depression in older patients. Devised by Yesavage in 1982[254], this was intended to be as simple as possible (yes/no answers instead of multiple choice) as it was felt that older patients became confused when faced with too many choices. The questions were carefully worded to avoid causing alarm or making patients defensive. There was also an effort to avoid focusing on somatic symptoms (as these would often be present in non-depressed older patients). It is scored from 0-15, and it is

felt that scores over 5 represent “caseness”. The tool is freely available from the Stanford University website. It has been validated in older renal patients, using the BDI-II as gold standard[248].

4.6.3 **Quality of life**

Quality of life is a nebulous term which encompasses both objective functional and psychosocial status, and subjective patient satisfaction with life. Accordingly, there are many quality of life scales in existence, and the emphasis of each varies depending on what it was initially designed to assess. The choice of which quality of life score to use will therefore depend very much on the aims of the research project.

The **SF-36** emerged from the Medical Outcome Study (MOS) by the Rand Corporation. A commercial version is now available, with the same questions but slight differences in scoring compared to the original (which is available free of charge on the RAND website). There are specific sub-domains for physical functioning (ADLs), role limitations due to physical health, role limitations due to emotional health, fatigue, emotional well-being, social role functioning, bodily pain, and general health perception. This is a very thorough questionnaire, but is rather long (36 questions) and therefore often has a high non-completion rate, particularly in older patients. It also emphasises ability to work and carry out physical tasks (as it was designed to assess quality-adjusted life years), which may not discriminate well between different levels of disability in chronically ill or older patients.

The **Kidney Disease Quality of Life Scale** (KDQOL) is another free RAND tool, based on the SF-36. There are two versions (long and short form). The short form consists of the first 12 questions in the SF-36, with additional questions about the intrusiveness of the kidney disease, and the presence or absence of renal-specific symptoms. The long form also contains questions about patient satisfaction with the renal service. This is therefore very well-suited for use in dialysis populations, but not always appropriate for CKD/transplant patients. Like the SF-36 it is fairly long, and this may lead to

higher non-completion rates. However there is less emphasis on working and on physical function that in the original SF-36.

By contrast, the **EQ-5D** (formerly Euroqol) survey has only 5 multiple-choice questions (mobility, self-care, usual activities, pain, depression) and a visual analogue scale (the patient records how good their health is today, out of 100). It is very quick and easy to complete. However it is not very detailed, and is also under copyright.

The **Palliative Care Outcome Scale** (POS)[255,256] was designed by the Palliative Care Core Audit Project Advisory Group at the Cicely Saunders Institute in London. It consists of 10 questions about pain, patient and family anxiety, adequacy of information, self-worth and personal affairs, and asks the patient to list their current main concern. It was designed specifically to fill the gap in outcome measures suitable for use in a palliative care setting, and as such is excellent for assessing how well the concerns of seriously ill and dying patients are being addressed, and how that is impacting on their subjective quality of life. It is a very different measure to the SF-36 and EQ-5D, with entirely divergent standards for judging quality of life, and as such should be used in quite different settings.

4.6.4 Comorbidity Indices

The **Khan Index**[109] was devised in 1993, based on the two-year survival of 375 patients with ESRF. Based on a combination of age and a number of comorbid conditions, patients are stratified into low, medium and high mortality groups. The drawback for our research is that all patients aged over 80 are automatically allocated to the high mortality group, leading to a "ceiling effect"[257].

The **Davies Score**[42] specifically excludes age, as it was designed to be used with age as an independent covariate. Points are given for a wide range of comorbidities, arguably making it a rather "blunt tool"[257] as many patients will score highly.

The **Charlson Comorbidity Index** (CCI)[258] was originally designed to predict ten-year survival for a patient with a range of comorbid conditions such as renal failure, ischaemic heart disease, HIV, etc. It therefore includes age as a variable. Each comorbid condition present is given a score which is weighted between 1-6 depending on its likely effect on mortality. For example, dementia is given a score of 1, while metastatic cancer has a score of 6. An extra point is given for each decade of life over age 40. It is worth considering that all of our patients will already have "renal failure" as a comorbidity, and as such will generally have life expectancies much shorter than 10 years. However a study comparing the ability of the Khan, Davies and Charlson scores to predict two-year mortality in ESRF patients found that the Charlson score has slightly better prognostic power than the other two scores (the Davies score when combined with age had similar predictive power, as one might expect)[259].

4.6.5 **Functional Status**

Numerous tools exist to quantify functional status, or physical functioning. These have been developed by different professions to measure different outcomes, and are therefore not necessarily equivalent. For example, the **Karnofsky Performance Scale** (KPS)[260] was initially designed for inpatient palliative care use. It ranks physical function from 100% (no symptoms) to 0% (dead). The KPS has been modified recently to reflect modern palliative care practice[261], with a focus on home-based care (Australia-modified KPS), and it is this version which we use in our study.

Other researchers have used the **Barthel Index**, which was initially designed by a physiotherapist to assess physical dependence in long-term inpatients[262]. It is used widely to measure ability to perform activities of daily living (ADLs) in a standardised, reproducible way, particularly in rehab settings (in order to track improvement in ADL functioning)[263]. It is rated from observation and has two items scored 0-1, six items scored 0-2, and two items scored 0-3, giving a total score from 0-20 (higher scores are more independent).

The **Katz ADL Scale**[264] is widely used in the US. This consists of a yes/no scale for the following 6-items: feeding; transferring; washing; dressing; toileting; continence. It is useful as a simple and standardised descriptor of dependence, however it is not detailed enough to measure small incremental improvements in functional status, such as in rehabilitation settings.

In contrast to basic ADLs, which are required for basic self-care, Instrumental ADLs (IADLs) are more complex activities required to live independently, such as shopping, housekeeping, managing money, food preparation, managing medications, using the telephone, using transportation. There are scales such as the **Lawton IADL scale**[265], an 8-item scale where each item is scored 0-4. Amusingly, in the original 1969 scale men were not scored on food preparation or housekeeping domains as they were not expected to be able to manage these things unaided. Current advice is to assess both genders on all domains. There is no clear consensus on which activities comprise IADLs – whether or not the individual patient is impaired will depend very much on what they personally need to be able to manage in order to live independently. Some other scales rely on patient interview (Frenchay Activity Index, Hamrin Activity Index[266]), however full Occupational Therapy assessment remains the gold standard.

4.6.6 Cognitive Function

Cognitive function is also an extremely complex domain to assess. Patients may be extremely cognitively impaired but still perform well in some areas on standardised screening. For example, in frontotemporal lobe dementia impulse control and executive function are significantly affected, but patients may remember facts extremely well. The gold standard assessment of cognitive function is a face to face interview with an old age psychiatrist or psychologist with a battery of cognitive function tests[267], but multiple shorter screening tools exist. It is important to note that these screening tools will not give a cause for the cognitive impairment, and in older renal patients this may be due to many causes[154], not limited to: uraemia; dementia (of which there are many causes);

delirium (which can persist for many months following the original insult); and of course depression. A collateral history from carers or family may also be extremely helpful.

The environment in which the assessment is carried out can make a significant difference to performance (loud, distracting or badly lit environments should be avoided)[268], and it is also worth remembering that many causes of cognitive function show diurnal variation. The patient should not be assessed when they are tired, have just woken from sleep or around mealtimes. They should also be assessed in a calm and emotionally non-threatening manner, letting the patient set the pace.

The **Mini Mental State Exam** (MMSE)[269] is one of the best-known screening tools. It was introduced by Folstein in 1975, and is very popular because it assesses a wide range of cognitive domains (orientation to time and place, short- and long-term memory, executive function, visuospatial ability, arithmetic, language). It consists of a wide variety of questions (naming items, drawing interlocking shapes, recalling items), takes about 10 minutes to administer, and is scored from 0-30 with scores between 19-24 considered mild impairment, between 10-18 considered moderate impairment, and below 9 considered severe. Performance on the MMSE is adversely influenced by education, age, language, and verbal ability. The MMSE also is criticized for taking too long to administer and score, and is also now (controversially) under copyright which has led to it falling out of favour with researchers in recent years[270].

The **Sweet 16**[271] assessment was introduced to avoid the copyright issues surrounding the MMSE. It is a 16-item assessment and unlike the MMSE it is not adversely influenced by age, language, and education. It takes about half as much time to administer and score as the MMSE. However later in 2011, Psychological Assessment Resources (PAR), the MMSE copyright holders, forced Sweet 16 to be withdrawn claiming copyright infringement due to similarities between the two assessments[270].

The **Montreal Cognitive Assessment** (MoCA)[272] has been suggested as a replacement. Like the MMSE it is a 30-item assessment which takes about 10minutes to complete and covers a wide range of domains. Scores below 27 indicate cognitive impairment. It has a greater emphasis than the

MMSE on executive function and attention. It is also more sensitive at detecting mild cognitive impairment than the MMSE, although less able to discriminate between moderate and severe dementia[273,274]. It is freely available on the internet and can be used in educational and clinical settings without permission, although the author requests that written permission is sought before it is used in research.

The Hodkinson **Abbreviated Mental Test** (AMT)[275,276] is a brief 10-point screening tool which is widely used to screen for impaired cognitive function, particularly in hospital inpatient settings. It is very quick, but tests only memory and orientation. As it is so short, it is not sensitive enough to track change in cognitive function over time for the purposes of most research studies.

Numerous other tools exist which examine specific facets of cognitive function, such as executive function, or visuospatial awareness.

4.6.7 **Distress**

Distress has been described as "the negative emotional experience of the individual" [277]. It is often assessed using patient interviews. It is a deliberately broad term - the concept of distress is intended to be more inclusive and less stigmatizing for patients than terms such as depression or poor quality of life. It recognises that the causes of distress can be manifold, from practical problems to symptoms.

In 1998 Roth et al[278] described a simple tool, the **Distress Thermometer** (DT), to identify distress associated with unmet need in cancer patients. It consists of a visual analogue scale (where 0= no distress and 10= severe distress) with prompts for possible practical, social, emotional and physical problems which may cause distress. The patient ticks any of these which may apply to them. The aim was to enable staff, who may often concentrate on physical health issues, to consider and discuss with patients their psychological and social needs.

DT scores have been shown to correlate with depression, low quality of life and high symptom burden in other studies[279-281]. The majority of published work on the Distress Thermometer has involved cancer patients[282-284], however several studies report its particular value in older patients[282,284-287], and those with other chronic diseases. Indeed, it has recently been adopted as part of the Gold Standards Framework (GSF) for Care Homes[288,289], a UK government-funded quality assurance programme to facilitate provision of quality care for residents nearing the end of life. The Distress Thermometer has also previously been evaluated in CKD patients as a tool to improve the recognition and management of patients' distress[290]. However it has not yet been formally validated in renal patients.

4.6.8 Minimum Data Set

All patients in Medicare-funded nursing homes in the US must complete this wide-ranging assessment annually. It examines functional status, cognitive function, psychosocial wellbeing, as well as comorbidities and medication histories. As such, it is widely used by US researchers as it is a large, pre-existing dataset.

4.7 The concept of "Distress"

There is a large body of research on distress in diseases such as cancer. However, the concept of distress is rarely unpacked. Much of this research presupposes that distress as a concept requires no further explanation.

Several definitions of distress do exist within the US cancer literature. The NCCN, in their "Distress Management" practice guidelines[291], define distress as: "A multifactorial unpleasant emotional experience of a psychological (cognitive, behavioural, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its

treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis" (p7). In the Clinical Journal of Oncology Nursing, Vitek et al[292] state that "Rather than a single physical or emotional symptom, distress can be multifactorial in aetiology and may represent physical, social, and emotional components" (p413).

In contrast to these broad definitions, many of the studies which use the distress thermometer to assess prevalence of distress in cancer patients make the assumption that distress is the same thing as depression or anxiety, using tests for depression as their comparator, and even using the terms interchangeably[279,284].

Steinberg et al[287] did investigate the relative importance of physical and psychological factors responsible for distress in lung cancer patients. They found that DT scores were highly correlated with depression and nervousness scores on the Edmonton Symptom Assessment Scale, and once these subscales were excluded there was little relation between DT scores and other ESAS subscales.

The UK Gold Standards Framework for Nursing Homes[288], which recommends using the DT as a screening tool for elderly care home residents, also conflates distress and depression. Stone et al[293] also review distress in older people, however they focus on the impact of living alone on distress. They use the GHQ-12, a self-report tool generally accepted to include three distinct constructs of 'Anxiety', 'Social dysfunction' and 'Loss of confidence'[294], to measure their concept of distress.

In renal literature, Ramer et al[295] focused on the prevalence of stressful life events in dialysis patients. This paper was novel in that it identified many different sources of distress for dialysis patients – only 50% of participants reported stressful life events related to their own health, with other common sources of stress including personal relationships and financial worries. However the impact of these stressful life events on the patients was not evaluated.

Gilbar et al[296] carried out structured interviews with haemodialysis patients to assess whether different coping styles affected psychological distress. They assessed distress using the Brief Symptom Inventory (BSI), which measures the severity of psychiatric symptoms. Although they do not define distress themselves, one may derive the implication that distress is a psychiatric phenomenon. In contrast, Chiou's Physical Symptom Distress Scale[297] is a self-report tool which assesses distress in dialysis patients by measuring physical symptom intensity, ignoring sources of psychological distress altogether.

Interestingly Gamondi et al[298] conflated the concept of distress with that of physical pain – distress being the response to experiencing pain. There are many similarities between the concepts of distress and pain, but I would argue strongly that they are not synonymous.

4.8 Why was this project needed?

CKD is a burden for older patients. It is associated with high mortality, high symptom burden, and poor quality of life. It is not clear whether we always pick up on patients' concerns, or intervene – for example depression is under-diagnosed in this group. This may be because patients don't tell us, or because we don't ask them.

It is also not always clear if our interventions (such as social worker referral, medication change or even starting dialysis) actually make any difference to how the patient feels. There have been several longitudinal studies to date which have assessed how functional status[101] and quality of life[17] change after initiation of dialysis. But these have been observational studies rather than intervention studies.

One problem with assessing patient wellbeing is that it is difficult to screen for all of the different factors which may cause distress within a fifteen-minute consultation. Patients, particularly older

ones, may also be conscious of “not bothering the doctor” and thus not mention their problems unless directly asked.

We introduced the Distress Thermometer, an ultrashort screening tool for psychological distress, into routine practice in our nephrology clinic, and pilot work reported that staff and patients found it helpful in focussing the conversation on the patient’s concerns rather than the doctor’s.

However, we encountered many questions about the Distress Thermometer (What is distress? Is this the same as depression? What is this actually measuring?). We also had questions ourselves (Does distress rise when patients start dialysis? Which patients are at higher risk of distress?). This project aimed to answer those questions.

In order for the Distress Thermometer to be accepted for widespread use within the renal community, it was necessary to clarify what exactly it measures – depression, high symptom burden, or something else? We also needed to be confident that the Distress Thermometer is reliable at measuring distress, and that results are reproducible. Our first study attempts to answer these questions.

In addition, it is not clear whether some subgroups (such as older patients, or those on haemodialysis compared with CKD4/5 patients) are more distressed than others, or whether factors such as anaemia or multiple comorbidities are associated with distress. The second study aims to address these issues.

The third study aims to provide more information about the trajectory of distress scores when either choosing haemodialysis or choosing not to dialyse. Does distress rise around the time of initiation of haemodialysis, and if so does it return to baseline over the succeeding six months? Are there patient factors (age, gender, comorbidity) which affect this? Previous work by other groups has examined trajectories of functional status in patients who have chosen not to dialyse[23], and trajectories of quality of life compared with survival in patients choosing to dialyse compared with those choosing conservative management[27].

Finally, we carried out a series of nineteen interviews with a broad range of dialysis and CKD4/5 patients. We explored their definition of and experience of distress, and how they had managed distressing experiences in their lives. We discussed their original diagnosis with CKD, the impact that their illness had had on their life and family, and what in terms of education and support would have reduced their illness-related distress.

4.9 Rationale for mixed methods approach

Traditionally there are two opposing research paradigms: the quantitative and the qualitative. The quantitative approach, or scientific method, measures data and attempts to prove or disprove hypotheses. It is excellent at providing a big-picture view of large groups of patients, and at answering yes/no or "countable" questions.

Qualitative work is able to explore phenomena in a depth which would not be possible to achieve with a standardised questionnaire, and allows for a multiplicity of narratives. Instead of large sample sizes and statistical tests, the design and conduct of the study, the internal and external validity of the findings, and their positioning within the existing literature are used to assess the quality of the work[299]. However the small sample sizes and lack of "objectivity" may make it difficult for quantitative researchers to accept the findings of qualitative research.

The "Mixed Methods" approach combines both quantitative and qualitative elements, in order to give a greater breath of understanding than could be achieved by either approach alone. In 1959 Campbell and Fiske[300] introduced the concept of "Triangulation", suggesting that by studying a phenomenon using multiple methods, one could be more certain that one's findings were not due to methodological artefact, in the same way that reproducibility is so important in quantitative studies.

Greene et al[301] reviewed a sample of 57 mixed methods studies, and identified four other purposes in carrying out mixed methods research (in addition to triangulation): *complementarity*, where

qualitative and quantitative methods are used to measure overlapping but different facets of a phenomenon; *development*, where the results obtained by one method inform the design of the other; *initiation* seeks to find paradoxes and reframe questions using new knowledge from the other method; and *expansion* seeks to increase the range of the research question by using different methods.

There are several different approaches to carrying out a mixed methods study[302]. The study may be quantitative-based with a minor qualitative aspect, qualitative-based with a minor quantitative aspect, or fully mixed. The synthesis of data may take place during data analysis, in the data-collection stage, or there may be full mixing of methodological worldviews and language. And the impetus for using a mixed methods approach may be driven by the research question itself, or by the researcher's methodological preferences.

There has been criticism of mixed method approaches from both sides of the paradigm wars. The paradigmatic differences inherent in mixed method research has led to accusations of lack of methodological rigor, and of fundamental incompatibility of the two paradigms. However the field has evolved, and there are now established frameworks for designing and evaluating mixed methods research[303,304].

5 Aims and objectives of the thesis

This thesis explores the phenomenon of distress in renal patients. What do patients mean when they talk of "distress?" Can we identify risk factors for distress? Does dialysis initiation cause distress, and if so is this potentially modifiable? We focus in particular on the use of the Distress Thermometer in renal populations – is it useful as a screening tool? What is it measuring?

The aims are:

1. To assess the construct validity of the Distress Thermometer by comparing agreement between DT scores and scores on other frequently-used depression and symptom scores, and to identify a threshold for "caseness" above which intervention should be considered.

2. To investigate potential risk factors associated with increased DT scores in both CKD4/5 and haemodialysis patients.

3. To assess the relationship between change in functional status and change in distress over time, in particular around time of dialysis initiation.

4. To explore patient definitions of distress, investigate patient-perceived causes of distress in CKD4/5 and dialysis patients, and to ask patients what we as healthcare professionals currently do, and what could we do differently, to mitigate this distress?

6 Validation of the Distress Thermometer in a UK Renal Population

6.1 Introduction

6.1.1 Aims of this study

1. To assess time taken to complete the DT, and to assess its acceptability to respondents
2. To assess construct validity of the DT by comparing agreement between DT scores and scores on other frequently-used depression and symptom scores
3. To identify a cut-off threshold for the Distress Thermometer (a score above which patients are likely to be a "case" on the BDI-II and HADS questionnaires), which may be used by clinicians or future researchers
4. To assess reliability of DT scores on repeat testing

6.1.2 Hypotheses

1. The DT may be completed quickly (<10mins) by UK renal patients, and is deemed acceptable by >75% of respondents.
2. The DT has moderate correlation with the Beck Depression Inventory II (BDI-II), Hospital Anxiety and Depression Scale (HADS), Memorial Symptom Assessment Score (Short Form) (MSAS-SF) and SF36 scores.
3. The cut-off DT score in renal patients is no different to that of non-renal patients in previous studies.
4. There is intra-respondent stability in DT scores over a two-month period, with ICC>0.60 ("good" reliability)

6.1.3 Outcomes of interest

DT, HADS, BDI-II, MSAS-SF and SF-36 scores

6.1.4 Study Design

We assessed construct validity of the DT by comparing agreement between DT scores and scores on a variety of symptom, depression and quality of life tools.

We then carried out a method comparison study to establish whether what DT score corresponded with 'caseness' for the BDI-II and HADS scores. We assessed intra-respondent stability of the DT by comparing the change in relationship between DT scores and scores on the BDI-II and HADS over a two-month period.

A smaller questionnaire study to gauge time taken to complete and acceptability of the Distress Thermometer was also carried out.

6.2 Methods

6.3 2.2 Methods

6.3.1 Research Ethics Committee Approval

Research ethics committee approval was obtained from Newcastle & North Tyneside 2 Research Ethics Committee (REC reference 13/NE/0087, see appendix for approval letter). The study was also included in the NIHR CRN Portfolio.

6.3.2 Study group

6.3.2.1 Study Setting

This was a two-centre study. The Royal Free NHS Foundation Trust in north London is an 840-bed acute hospital trust with a large tertiary renal department providing CKD, haemodialysis, peritoneal dialysis and transplant services to north central London across both the main hospital and five satellite units. It has 1500 CKD4/5 patients who attend regular outpatient clinics, and approximately

450 prevalent haemodialysis patients. It serves an ethnically diverse community, encompassing both very wealthy and very deprived boroughs.

In contrast, the Lister Hospital is a 730-bed district general hospital providing acute services for the rural and suburban counties of Hertfordshire and south Bedfordshire. Its renal department provides CKD, haemodialysis and peritoneal dialysis services across the main site and four satellite units, but does not have an acute transplant service. It has approximately 1000 CKD4/5 patients, and 450 haemodialysis patients. It serves a majority white British population which is predominantly middle-class, although there are pockets of deprivation.

6.3.2.2 Study Population

All patients attending Lister Hospital and Royal Free Hospital nephrology outpatient low clearance clinics (CKD 4/5) and outpatient haemodialysis units were screened for eligibility for the study. Unfortunately due to the small size of these hospitals' peritoneal dialysis cohorts, a separate PD arm would not have been able to recruit enough patients to be adequately powered, and there is evidence that PD patients and HD patients are sufficiently heterogenous[17] that a combined RRT arm would have been methodologically unsound.

6.3.2.3 Inclusion Criteria

Attending either Lister or Royal Free Hospital low clearance clinic or haemodialysis unit.

Aged >18 yrs.

No upper age limit.

6.3.2.4 Exclusion Criteria

Inability to consent

Unable to understand or complete Distress Thermometer (DT)

Unable to comprehend written English (BDI, HADS, MSAS and SF-36 are written tools; translation into other languages is a lengthy process requiring multiple cross-checks if validity is to be maintained in the new language[305]).

6.3.3 Sample size calculation

There were three main problems when carrying out a sample size calculation – firstly, there is no existing data on the sensitivity or specificity of the Distress Thermometer for detecting depression in renal patients as it has not previously been used in this patient group. Secondly, the prevalence of depression in this group of patients has been calculated as anywhere between 15-35%, making the coefficient (k) of cases to controls in a random sample anywhere between 1.86 - 5.67. Finally calculation of sample sizes for Receiver Operator Curve (ROC) studies is complex[306-308], and is rarely done[248,251,253,309]. This means that there were few prior studies to use as models.

The Hanley and McNeil sample size calculation formula[310], in conjunction with the worked examples provided by Hajian-Tilaki's review paper[306], was used to calculate sample size. From a review of the literature, this method appears to be extremely well-respected[306,308] and the original paper has over 15000 citations on PubMed.

First the VF, or variance function, was calculated using the highest and lowest likely values of k shown above:

$$VF = \left(0.0099 \times e^{-A \times A/2}\right) \times [(5 \times A^2 + 8) + (A^2 + 8)/k]$$

Where A is the parameter from the binomial distribution, calculated below:

$$A = \varphi^{-1}(AUC) \times 1.414$$

$$= (0.95^{-1} \times 0.80) \times 1.414$$

$$= 1.191$$

Where φ^{-1} represents the inverse of the cumulative normal distribution function. An estimated AUC of 0.80 was chosen, as previous studies have shown similar or higher AUCs when evaluating depression scores in renal patients[248,249,251,253], and DT scores in non-renal patients[280,283,286]:

So $VF = \left(0.0099 \times e^{-1.191 \times 1.191/2}\right) \times [(5 \times 1.191^2 + 8) + (1.191^2 + 8)/k]$

When k = 1.86, VF = 0.064

When k = 5.67, VF = 0.021

Then the number of "cases" required was calculated, as shown below:

$$N = \frac{\left[Z_{\frac{\alpha}{2}}^{2} \times VF\right]}{L^2}$$

Where N= number of cases, $Z_{\alpha/2}$ is 1.96 for a 95% confidence interval, VF is the variance function, and L is the desired half-width of the confidence interval, in this case 0.05. This gives the number of cases needed as:

$$N = (1.96^2 \times VF) \div 0.05^2$$

$$N = 3.84 \times VF \div 0.0025$$

When k = 1.86, $N = \frac{(3.84 \times 0.064)}{0.0025}$ = 99

When k = 5.67, $N = \frac{(3.84 \times 0.021)}{0.0025}$ = 33

(rounded up to nearest whole number as one cannot be a partial “case”)

The total sample size can be calculated as follows:

$$N \times (1 + k)$$

When k = 1.86, $N = 284$

When k = 5.67, $N = 220$

Therefore 220-284 participants would be needed, depending on the prevalence of depression in this population.

6.3.4 **Recruitment**

6.3.4.1 Research Team

The research team at the Royal Free comprised Helen Alston (HA); Aine Burns (AB), my supervisor and lead consultant for Low Clearance, who was study Primary Investigator (PI); and the Royal Free’s team of renal research nurses.

The research team at the Lister comprised a renal counsellor with extensive research experience in dialysis quality of life (who was Site Lead); a renal consultant; and a renal social worker.

All members of both research teams were up to date with Good Clinical Practice (GCP) and NHS Information Governance training.

6.3.4.2 Low Clearance Clinics

Potentially eligible patients were identified by a member of the research team from outpatient clinic lists using the electronic patient record. The patient information sheet and a covering letter were sent to all eligible patients with their clinic appointment letters. Patients were then approached in the clinic waiting room on arrival for their routine appointment, and asked if they were interested in

taking part. Inclusion and exclusion criteria were re-confirmed with the patient. English language skills and cognitive skills were informally assessed by the researcher during the recruitment process, as these exclusion criteria were not always well-documented on the electronic patient record.

If they expressed interest, they were provided with written information about the study, and given up to fifteen minutes to consider the study and to ask questions. Those who were happy to proceed were asked to provide written consent. If more time was requested, they were approached again at their next appointment (usually one month later). There was also a contact telephone number on the patient information sheet if they, or any of their family or friends, had any questions for the research team. Patients who refused to take part in the study were not approached again.

6.3.4.3 Haemodialysis Patients

Potentially eligible patients were identified by a member of the research team from the dialysis schedule, and were discussed with the patient's named nurse to confirm that the patient met the inclusion and exclusion criteria for the study (named nurses generally know their patients extremely well and would be aware of any cognitive impairment or insufficient English language skills even when these were not documented on the electronic patient record).

All eligible patients were given a patient information sheet and a brief explanation of the study by one of the researcher team at their routine dialysis session, with the opportunity to ask questions. They were then given a week to consider whether or not they would like to take part. There was also a contact telephone number on the patient information sheet if they, or any of their family or friends, had any questions for the research team.

A researcher approached them at a subsequent dialysis session one week later to confirm whether or not they would like to take part, and to answer any further questions. If patients wished to take

part in the study, they were asked to provide written consent. Patients who refused were not approached again.

6.3.5 **Data**

6.3.5.1 Reference standards

The reference standards for the study were three widely used screening questionnaires standardised for use with physically ill patients, all of which have been previously validated in renal patients:

- HADS - 14-item measure that gives scores for 'possible' and 'probable' anxiety and depression. When a global score was used, a case for 'emotional distress' was defined as >12 in renal patients[251].
- Beck Depression Inventory II – a depression tool containing 21 questions, each answer being scored on a scale value of 0 to 3. A cut-off of >13 was used to detect "caseness" in renal patients. Higher total scores indicate more severe depressive symptoms.
- Memorial Symptom Assessment Scale (Short Form) - symptom assessment scale which measures frequency and distress of 32 highly prevalent symptoms
- SF-36 – a quality of life tool consisting of 8 scaled scores: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional functioning, social functioning, and mental health.

Copies of these reference questionnaires may be found in Appendix B.

A short acceptability questionnaire was also administered. This consisted of three closed questions (the time taken to complete the DT, if participants were upset by completing it and if they consider any changes are needed to its format or content) and an open question for further comments.

6.3.5.2 Data Collection

In order to assess sensitivity to change over time, all 5 tools were administered together on three occasions: three consecutive clinic visits (baseline, 4-6 and 8-10 weeks) for low clearance patients, and at start of three dialysis sessions (each a month apart, on same day of week to avoid changes in patient distress due to differences in volume status/uraemia) for dialysis patients.

It is known that performance on neuropsychiatric tests may fluctuate before, during and after dialysis, with best performance in cognitive tests achieved 24hrs after a dialysis session[311-313] (this is thought to be due to a combination of low uraemic toxins in the blood following dialysis, and recovery from the cerebral hypoperfusion which frequently occurs during dialysis sessions). It is possible that symptoms and low mood may also fluctuate in a similar manner. It is also possible that distress levels may be different during dialysis sessions than at other times of the week (distress may be higher, because the participant does not find dialysis enjoyable. Or it may be lower, if the participant has troublesome symptoms related to fluid overload which they know the dialysis session will improve). We therefore aimed to complete the reference questionnaires at the same time for each patient, in order to minimise this variability.

6.3.5.3 Data handling and record keeping

Names, hospital numbers, dates of birth and genders of patients, along with responses to the questionnaires, were collected from patients in accordance with the patient consent form, patient information sheet and the study protocol.

The data was collected electronically for statistical analysis using Excel 2010 (Microsoft) and the statistical package STATA/IC 12.1 (StataCorp LP). University College London acted as the data controller for the study.

I processed, stored and disposed of the patient demographic information and questionnaire results in accordance with the Data Protection Act 1998, and with NHS data protection guidelines. Royal Free patient data was stored centrally at the Centre for Nephrology: the hard copies of questionnaires were stored in a locked filing cabinet with access controlled by me, and the database was stored on password-protected UCL computers in a secure office (requiring swipecard access), and on an NHS-issued encrypted USB stick (for transfer between NHS sites only).

Hard copies of Lister patient questionnaires were stored in a locked filing cupboard in the Lister renal research department, and electronic data transferred to me via encrypted NHS.net email. The patient data was not transferred to any party except those identified in this protocol and was not processed and/or transferred other than in accordance with the patients' consent. At the end of the study, the patient questionnaires and consent forms were sent for local NHS archiving.

6.3.6 Statistical methods

6.3.6.1 Receiver Operating Characteristic Curves

A Receiver Operating Characteristic (ROC) curve shows the diagnostic ability of a test as the discrimination threshold is varied (ie as the score for "caseness" changes)[314]. The points on the curve are created by plotting the sensitivity against the false positive rate (1-specificity) for each different threshold level.

The curve begins at 0,0 the diagnostic threshold at which all subjects test negative for the disease, and ends at 1,1 the threshold at which all subjects test positive. The straight diagonal line connecting these two points represents a dummy test with no ability to distinguish between cases and non-cases (ie random chance). The further the ROC curve lies away from this diagonal (ie the greater the area under the curve (AUC) is), the greater the diagnostic accuracy of the test under evaluation.

6.3.6.2 Regression analysis

In simple linear regression we regress the outcome of interest onto a single explanatory variable (exposure). This regression provides us with a constant (intercept of the line of best fit, ie the expected observed value when the exposure = 0), and a value for the slope. This can be expressed by the equation y = a + bx where "y" is the observed outcome, "a" is the constant, "b" is the slope, and "x" is the exposure.

Multivariable regression can adjust for many variables at the same time, accounting for different types of outcome and independent variables. We can then test which of several potential models best fits the observed data using the likelihood ratio test (the likelihood of any value of a parameter compared to the likelihood for the most likely value, ie the maximum likelihood). The advantage to the likelihood ratio test is that a null hypothesis for a parameter can then be tested.

6.3.6.3 Multi-level modelling

Classical statistical techniques and regression models both share the assumption that individual observations are statistically independent of each other. In other words, there is no correlation between individuals.

However, when we consider repeated measures on the same individual (such as repeated DT scores over time), this assumption is not valid. We would expect scores from the same person to be more similar than scores from different people, ie there would be correlation between them. This is known as clustering of data (clustering may also be seen when individuals are recruited from the same clinic or family, or share other characteristics which make the correlation of observations within the cluster greater than the correlation between clusters).

To take account of this clustering, specific statistical methods must be used (use of classical methods will produce confidence intervals that are too narrow and P-values that are too small). In this study I

have used fixed and random effects models (also called mixed models, or multi-level models), but other methods such as Generalised Estimating Equations (GEE) and Robust Standard Errors may also be used. The proportion of correlation between individual observations within a cluster (the Intra-Cluster Correlation Coefficient, ICC) can also be calculated.

Multi-level models consist of fixed effects and random effects. When constructing multi-level models, we can specify whether the intercept in the model should be fixed or allowed to vary at the cluster level (fixed slope, random intercept model) or whether both the slope and intercept should be allowed to vary (random slope, random intercept model). Likelihood ratio testing is then used to confirm which model best fits the data.

6.3.6.4 Statistical approach used in this study

Descriptive analysis

Data were analysed using STATA/IC 12.1 (StataCorp LP). Histograms were plotted to show the distribution of scores for the DT and each of the reference questionnaires and their subscales. Summary statistics such as mean and median scores were calculated.

Construct Validity

The DT was non-normally distributed, so correlation between the DT and the reference questionnaires was assessed using Spearman's Rank Correlation Coefficient. Two-way scatter graphs were plotted to give a visual indication of correlation.

Method-comparison (identification of "cut-off' threshold)

ROC curve analysis was used to examine the sensitivity and specificity of the DT scores against the cut-off scores already shown to demonstrate clinically significant symptoms ('caseness') in the HADS

and BDI-II tools. We chose a cut off of 12 for the HADS and a cut off of 13 for the BDI-II; these values were obtained from the Loosman study[251] which simultaneously validated both the BDI-II and the HADS in renal patients, so that the threshold for 'caseness' used for both tools were validated against the same gold standard (psychological interview). The MSAS-SF and SF-36 tools do not have a threshold score for 'caseness' so were not included in this part of the analysis.

Intra-respondent reliability

Sensitivity to change was assessed using multilevel models. First the trajectories of DT scores, HADS scores and BDI-II scores over the three visits were graphed. Then linear regression of DT scores by visit number was carried out, to assess how DT scores changed between visits. Random intercept and random slope models were compared using likelihood-ratio tests, Intra-class Correlation Coefficients (ICCs) were calculated. Similar models were produced for HADS and BDI-II scores, in order to compare stability over time of the DT with stability over time for the HADS and BDI-II.

Following this, the relationships between DT and HADs and BDI-II scores over time were examined. Random intercept and random slope models of DT by HADS and DT by BDI-II scores were compared using likelihood-ratio tests.

Time taken to complete, and acceptability

Frequencies, medians and inter-quartile ranges were used to describe the time taken for patients to complete the DT, the number of participants upset by it and who feel that changes are needed.

Content analysis was used to identify themes from participants' qualitative responses, highlighting both advantages and disadvantages of the tool.

6.3.7 Withdrawal and Missing Data

When responses were missing, the entire tool that data was missing from was excluded from the analysis but the other completed tools provided by that patient were used. We used pairwise deletion during the statistical analysis where data was missing.

Consent was reconfirmed at each of the three clinic visits that data was to be collected at. If participants withdrew consent to continue with the study, data from previous visits was still included assuming the participant remained happy for us to do this. If they withdrew consent completely, all of their data was removed from the study. If capacity to consent was lost between study visits, data from previous visits (when they were still able to consent) was used, but we did not collect any further data.

6.3.8 Ethical Considerations

Research Ethics Committee (REC) approval for both this and the following cross-sectional study (chapter 4) (which uses the same dataset) was obtained (see Appendix A). Fully informed written consent was obtained from all participants in line with Good Clinical Practice (GCP) guidelines, as described above. Data was treated confidentially as per the Data Protection Act (1998).

Patients who expressed suicidal ideation or whose scores on any of the reference tests gave cause for concern were discussed with a senior clinician in the research team and appropriate action was taken. This included urgent (same day) review by a member of the clinical team, referral on to renal clinical psychology services, or hospital admission.

6.4 Results

6.4.1 Recruitment and participant characteristics

We recruited 324 patients (158 in the CKD4/5 cohort, 166 in the HD cohort). The median age was 67 years (IQR 50.25 – 76.48). 69% of participants were male. The mean age was 63 years, ranging from 19 to 93 years with an interquartile range of 50 to 76 years. These are in keeping with our two centres' renal populations, and also reflect the demographics of the UK renal population as a whole *(UKRR 17th Annual Report[315]).*

6.4.2 Study withdrawal/loss to follow up

We received 324 completed first-visit questionnaires (100% completion rate – this is to be expected as the vast majority of the first-visit questionnaires were completed at the same time as consent was taken). There was a substantial loss to follow up between first and subsequent visits (see Table 6.1 Loss to follow up over three visits, by modality).

The loss to follow up was greater in the CKD4/5 arm, despite the higher mortality associated with haemodialysis. This is likely due to the "captive audience" on haemodialysis; the participants attend dialysis sessions three times a week on a predictable schedule, so were easy to locate for follow up. In addition, each dialysis session lasts between 3-5 hours, so participants were often happy to pass the time by taking part in research.

In contrast, the CKD 4/5 patients were sometimes missed when clinic appointments were cancelled or rearranged at short notice. Some participants completed the research questionnaires in the clinic waiting rooms, but others preferred to complete them at home and post them back, with a resulting lower completion rate (as expected with postal surveys, which have an average response rate of around 17%[316,317]).

Figure 6.1 Recruitment Flowchart

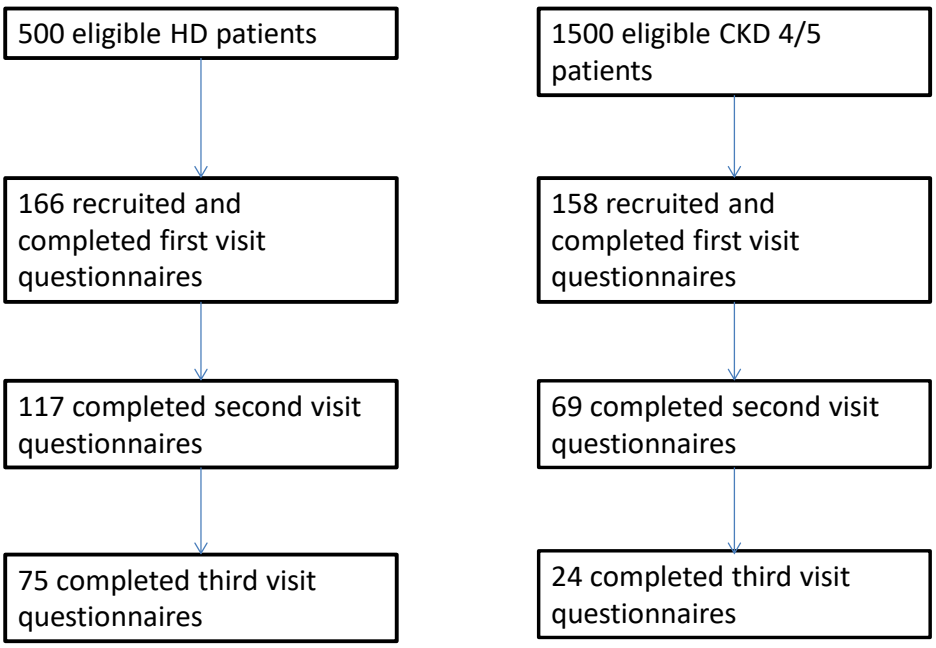


Table 6.1 Loss to follow up over three visits, by modality

	Visit number		
	1	2	3
CKD 4/5 cohort	158 (100%)	69 (44%)	24 (15%)
HD cohort	166 (100%)	117 (70%)	75 (45%)
Total	324 (100%)	186 (57%)	99 (31%)

Table 6.2 Characteristics of study population

	N= 324
Mean age (years)	63 (IQR 50-76)
Gender	69% male

6.4.3 Descriptive analysis of questionnaire scores

Distress Thermometer scores

Figure 6.2 shows the distribution of Distress Thermometer scores across the whole study cohort. The mean DT score was 3.5, with a median of 3 and an interquartile range of 1-5. Figure 6.3 shows the distribution of scores stratified by treatment modality (CKD 4/5 or haemodialysis). The haemodialysis group have a higher median distress score (median DT score 4 for HD patients compared with 2 for CKD patients) – this is analysed in more detail in Chapter 5.

Figure 6.2 Distribution of DT scores (median = 3)

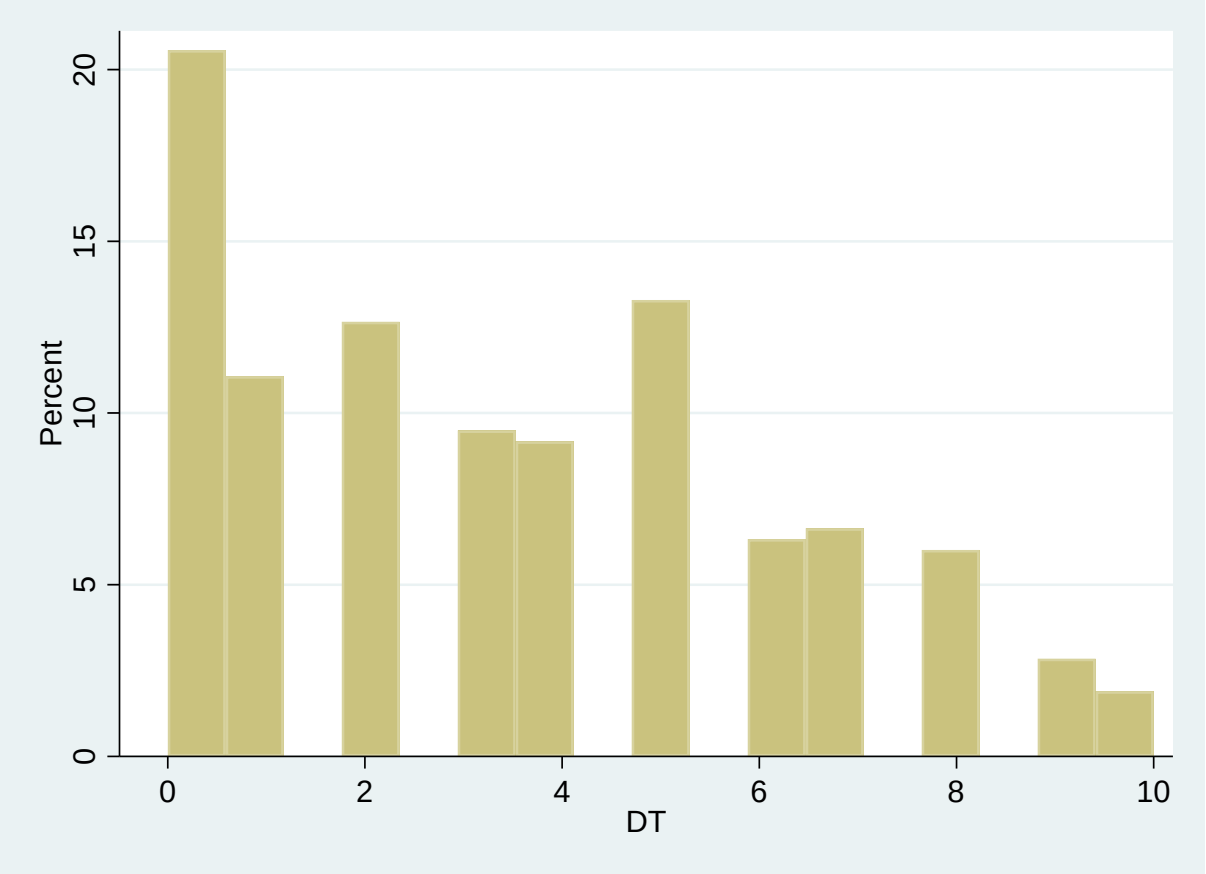
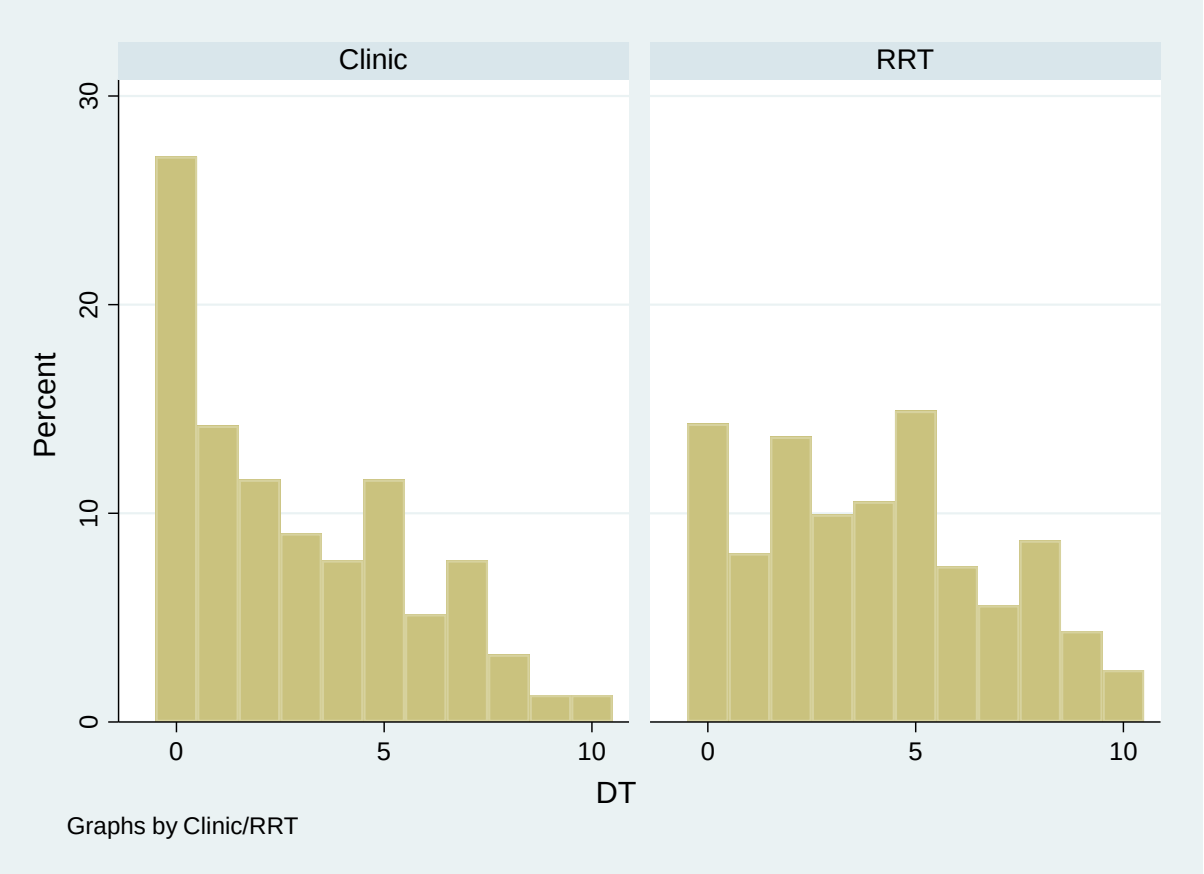


Figure 6.3 Graph to show distribution of DT scores by modality (median DT score for CKD 4/5 patients = 2, median DT score for HD patients = 4)



HADS and BDI-II scores

The median HADS score was 7, with an IQR of 3-13. 97 patients (30%) had a HADS score ≥12 (ie met the criteria for 'caseness') (

Figure 6.4). 106 patients (33.5%) had a BDI-II score ≥13 (Figure 6.5). This suggests that between 30-35% of the participants would have been assessed as possibly being depressed using these two established screening tools (25% of participants were 'cases' on both screening tools, see Table 6.3). This suggests relatively good, but not perfect, agreement between the two questionnaires (the differences between the two questionnaires are discussed in Section 4.6.2).

Figure 6.4 Distribution of HADS total scores (median score = 7, “Case” ≥ 12)

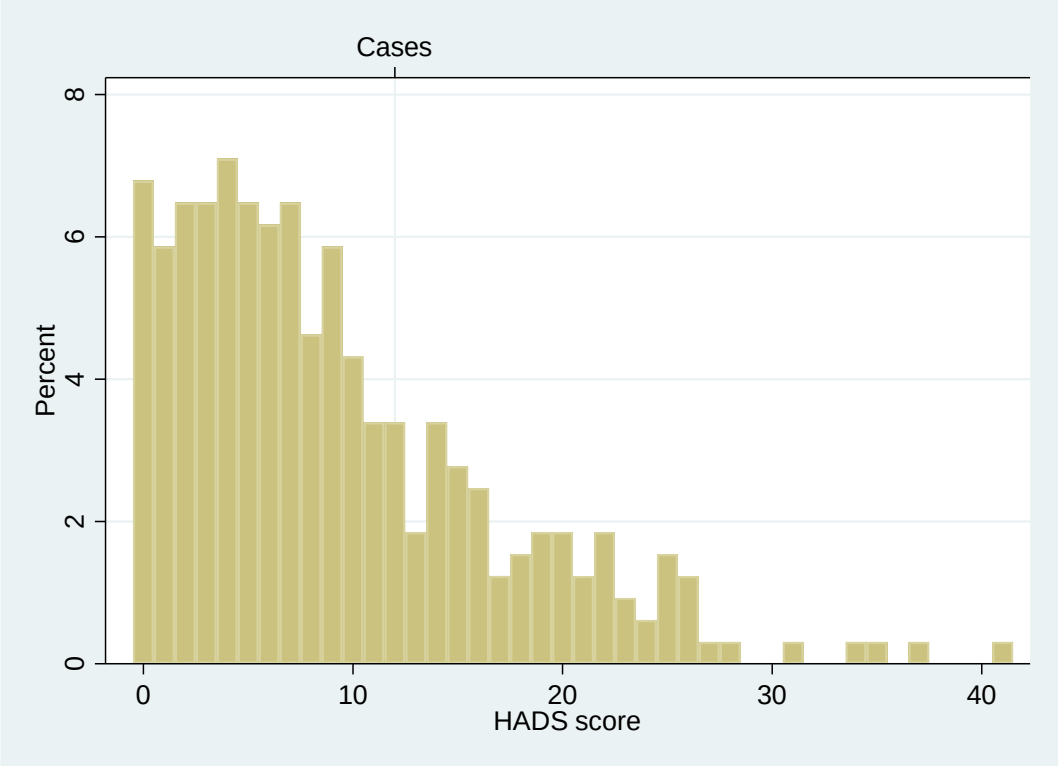


Figure 6.5 Distribution of BDI scores (median score = 8, “Case” ≥ 13)

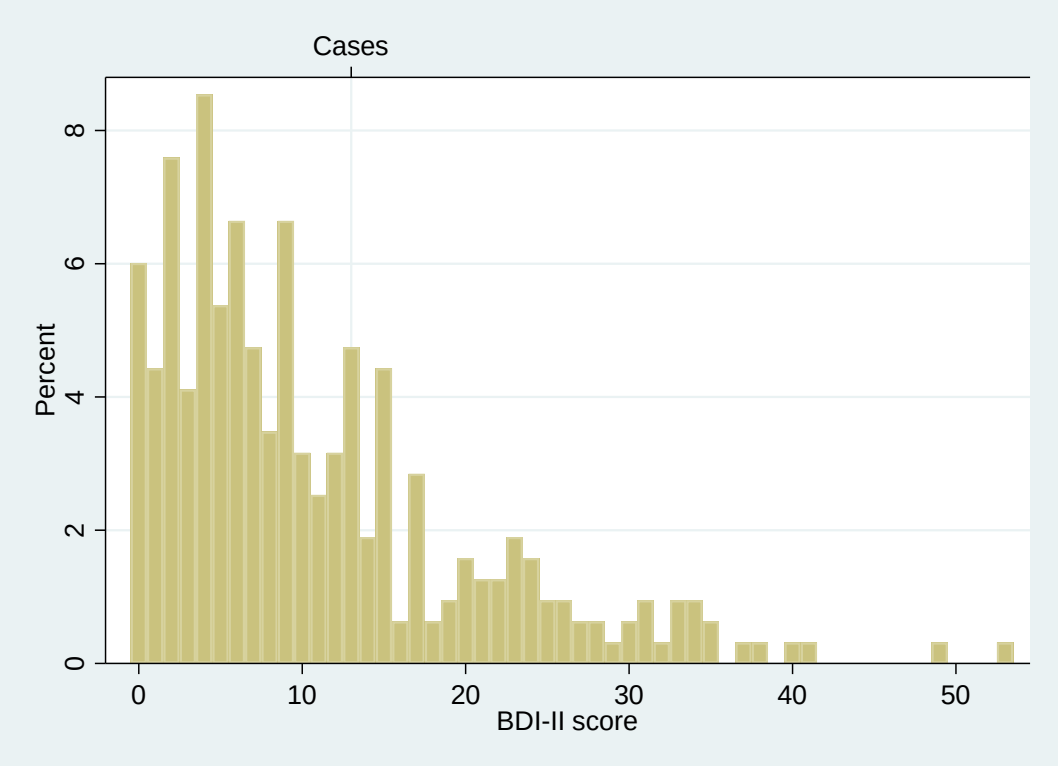


Table 6.3 Two-way table showing 'cases' of depression using HADS and BDI-II questionnaires

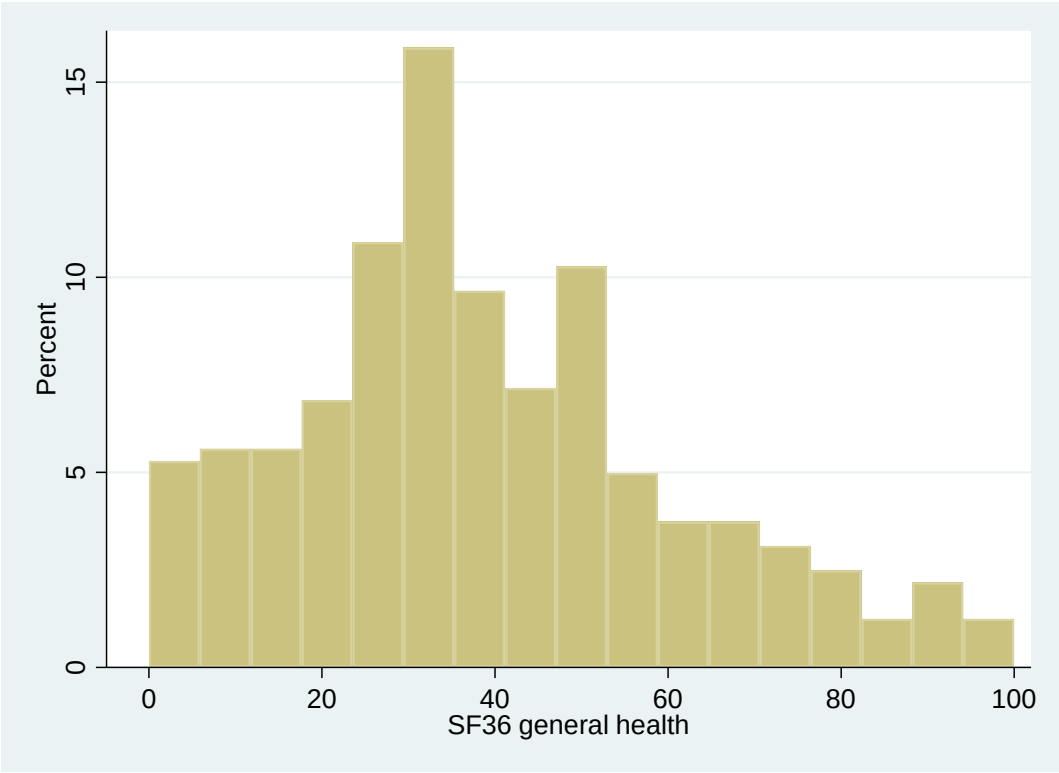
		BDI-II		Total
		Not case	Case	
HADS	Not case	193 (60%)	34 (10%)	227 (70%)
	Case	17 (5%)	80 (25%)	97 (30%)
Total		210 (65%)	114 (35%)	324 (100%)

Pearson chi2(1) = 135.7619 $P < 0.001$

MSAS-SF scores

The mean number of symptoms reported using the MSAS-SF was 1.03 per participant overall, however dialysis patients reported almost twice as many symptoms as CKD patients (1.33 symptoms per dialysis patient versus 0.71 symptoms per CKD patient). The distribution of total MSAS-SF scores (ie number of symptoms weighted by severity) shows a skewed normal distribution, with a mean score of 19 and median of 15 (Figure 6.6 Distribution of MSAS scores (median = 15)Figure 6.6). This suggests that, while the majority of participants report few symptoms, a minority of patients have a large number of severe symptoms.

Figure 6.6 Distribution of MSAS scores (median = 15)



SF-36 subscale scores

Figures 6.7 – 6.14 show the distribution of scores for each of the eight subscales of the SF-36. For each, a higher value represents better health.

Figure 6.7 shows the distribution of scores for the Physical Role subscale. This represents ability to carry out daily activities. We found a bimodal distribution, with large numbers of participants describing a significant limitation in their ability to carry out daily activities due to physical limitations. It is recognised that the SF-36 has a 'floor' effect in older participants (when a measure possesses a distinct lower limit for potential responses and a large concentration of participants score at or near this limit).

Figure 6.8 shows the distribution of scores for the Emotional Role subscale, representing limitation in daily activities due to emotional or psychological problems. Again, a substantial proportion reported significant limitations.

Figure 6.9 shows the distribution of scores for the Energy subscale. There is a fairly normal distribution of scores around a mean of 47, suggesting that, while participants' energy levels show a wide variability, the majority feel that their energy levels are impaired to some extent.

Figure 6.10 shows the distribution of scores for the Emotional Wellbeing subscale. The majority of participants reported good emotional wellbeing.

Figure 6.11 shows the distribution of scores for the Physical Functioning subscale. Like the Energy subscale there are a wide range of reported scores, with apparent peaks around 20%, 60% and 90%.

Figure 6.12 shows the distribution of scores for the Social Functioning subscale. There appear to be two peaks – one at 50% and another at 100%.

Figure 6.13 shows the distribution of scores for the Pain subscale. Although 34% of participants score 100% (indicating no impact of pain on their quality of life), a substantial tail of participants

have much poorer scores. This is in contrast to the MSAS-SF results, which indicated that these patients have few symptoms.

Figure 6.14 shows the distribution of scores for the General Health subscale. This appears to be normally distributed around a mean of 39, suggesting poor overall health in this cohort.

Figure 6.7 Distribution of SF 36 Physical Role subscale scores

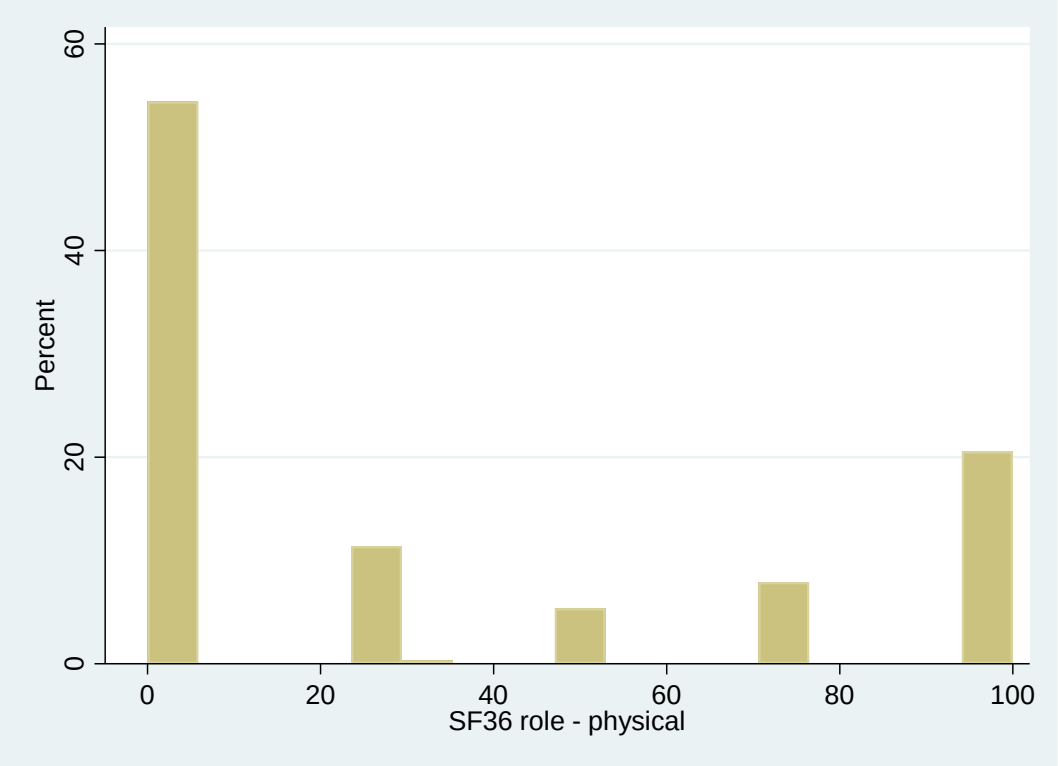


Figure 6.8 Distribution of SF 36 Emotional Role subscale scores

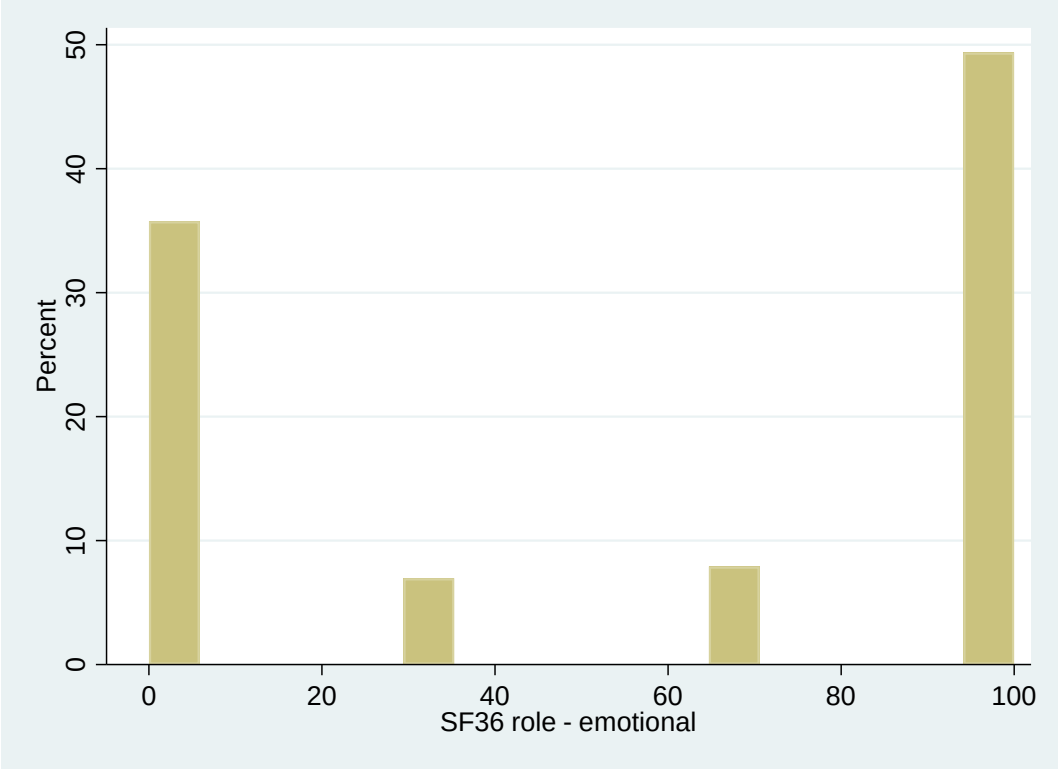


Figure 6.9 Distribution of SF 36 Energy subscale scores

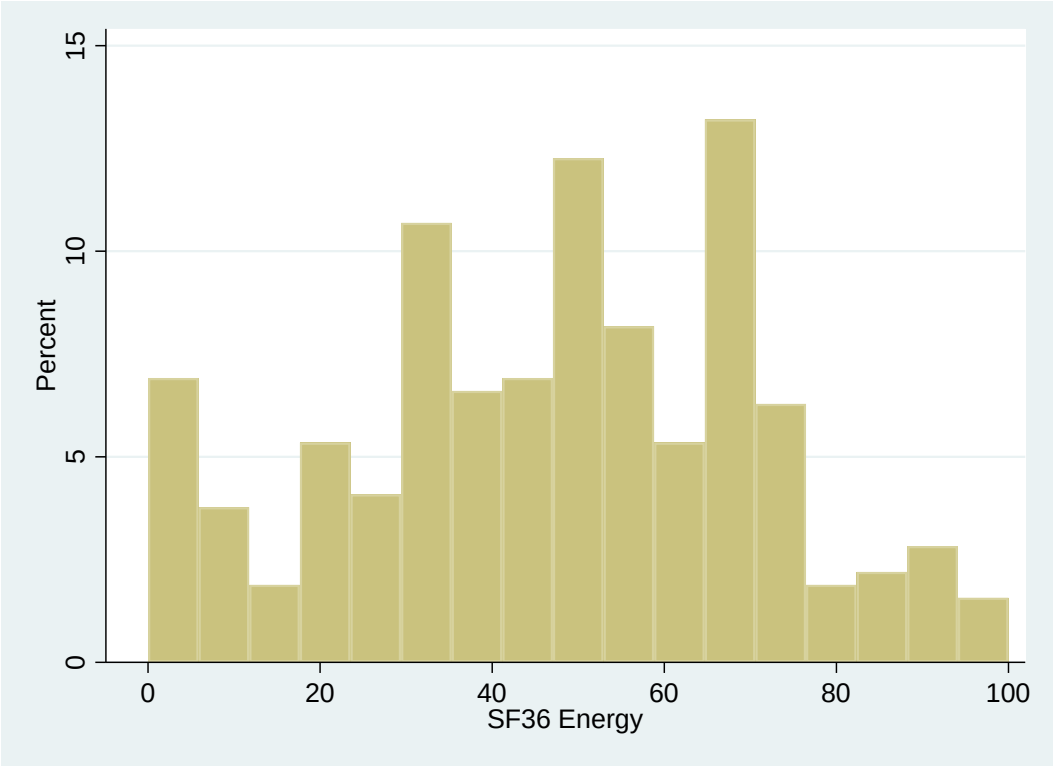


Figure 6.10 Distribution of SF 36 Emotional Wellbeing subscale scores

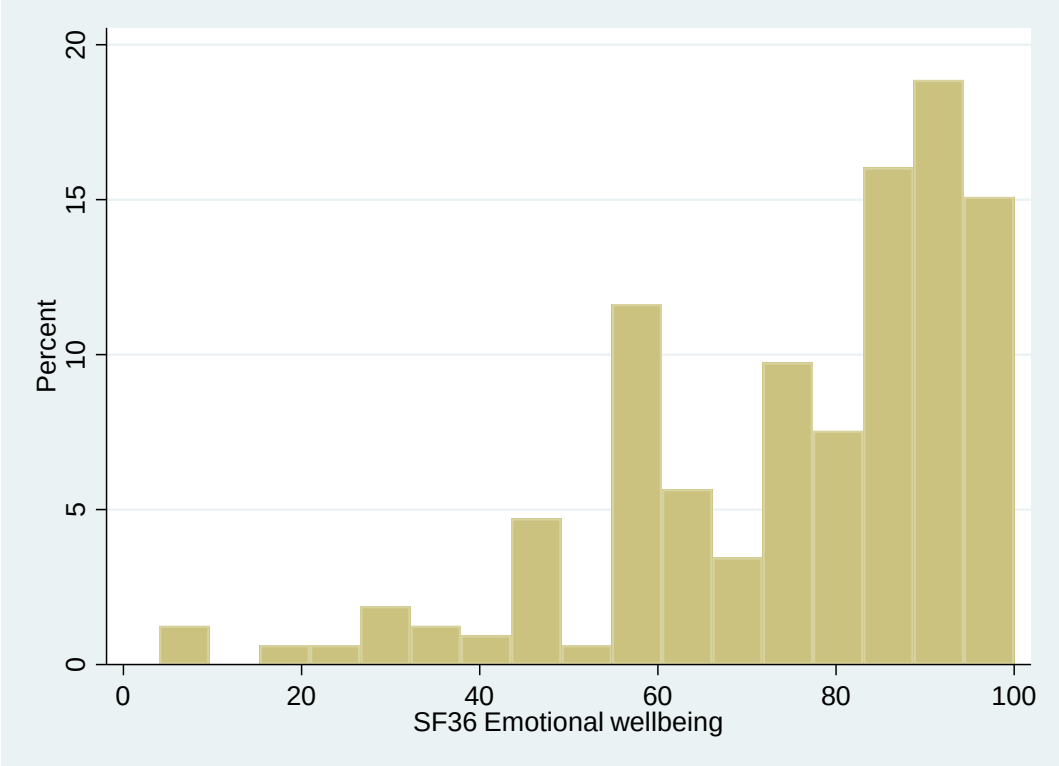


Figure 6.11 Distribution of SF 36 Physical Functioning subscale scores

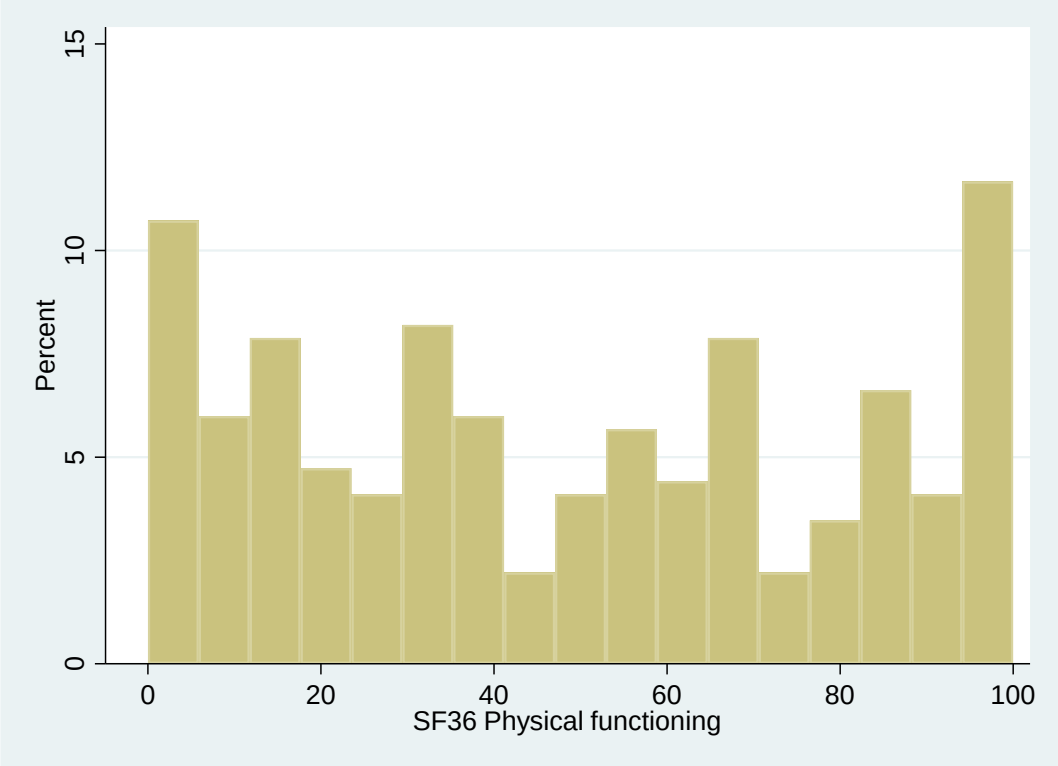


Figure 6.12 Distribution of SF 36 Social Functioning subscale scores

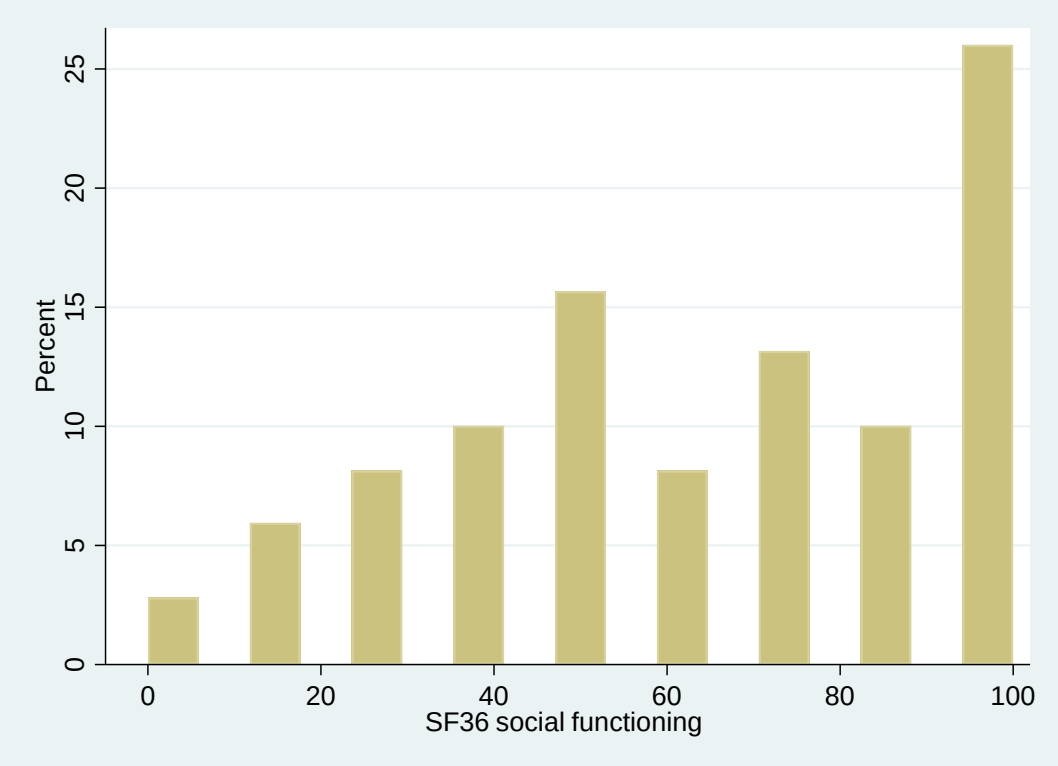


Figure 6.13 Distribution of SF 36 Pain subscale scores

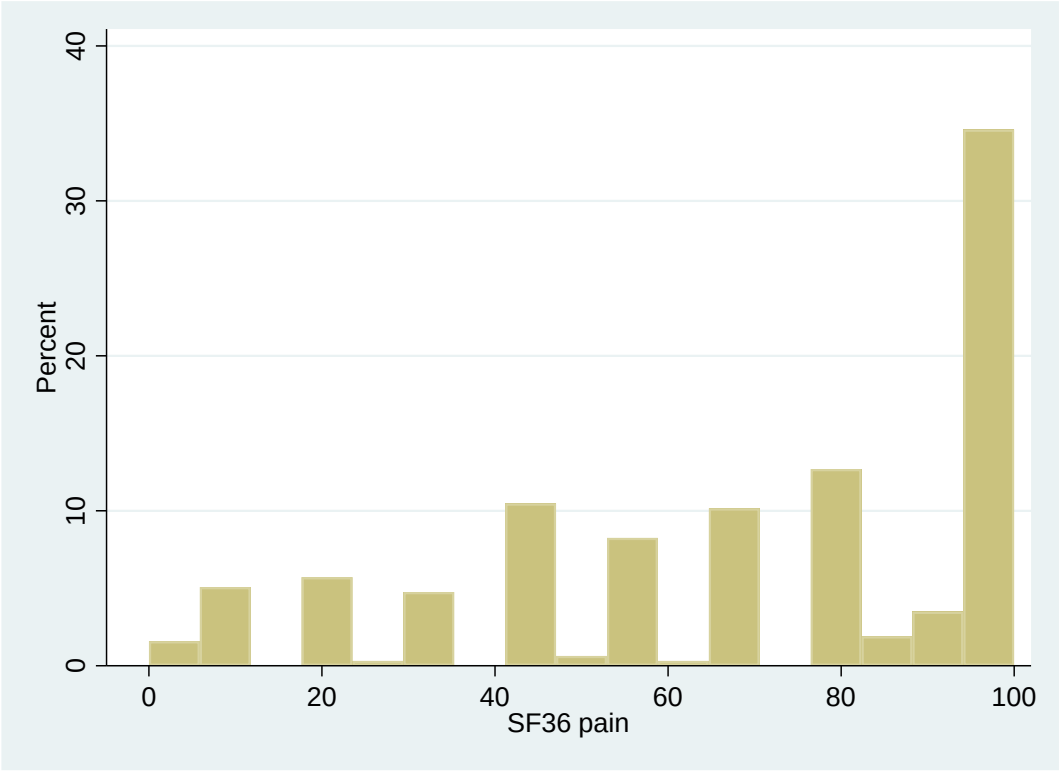
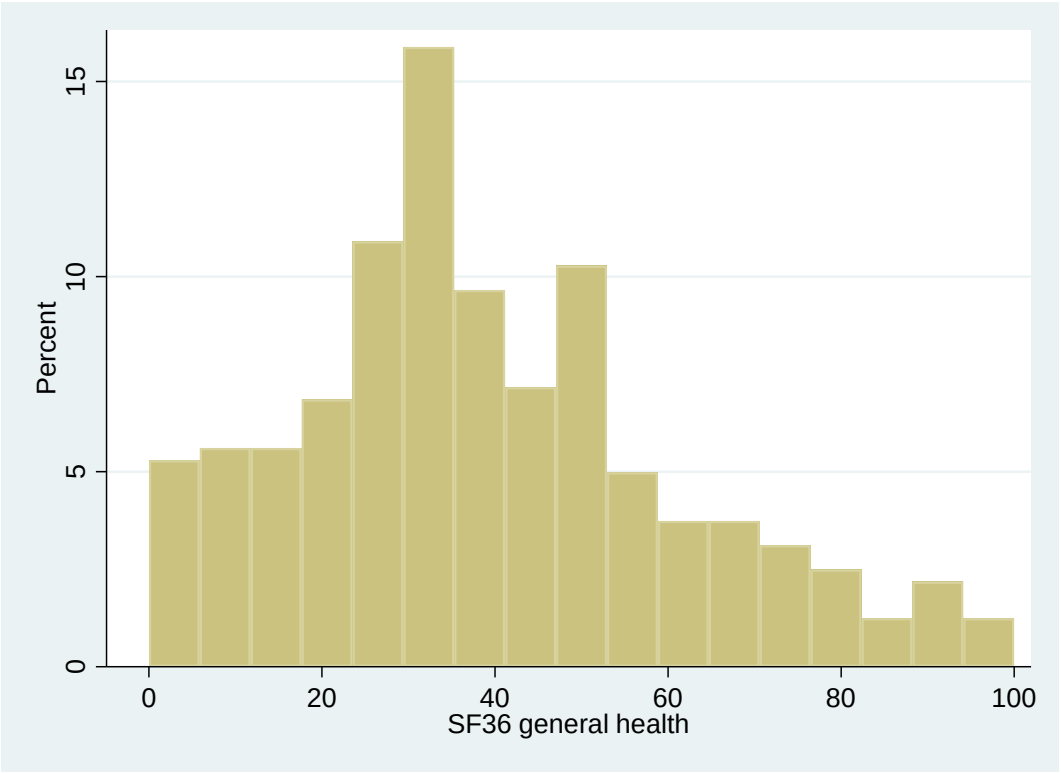


Figure 6.14 Distribution of SF 36 General Health subscale scores

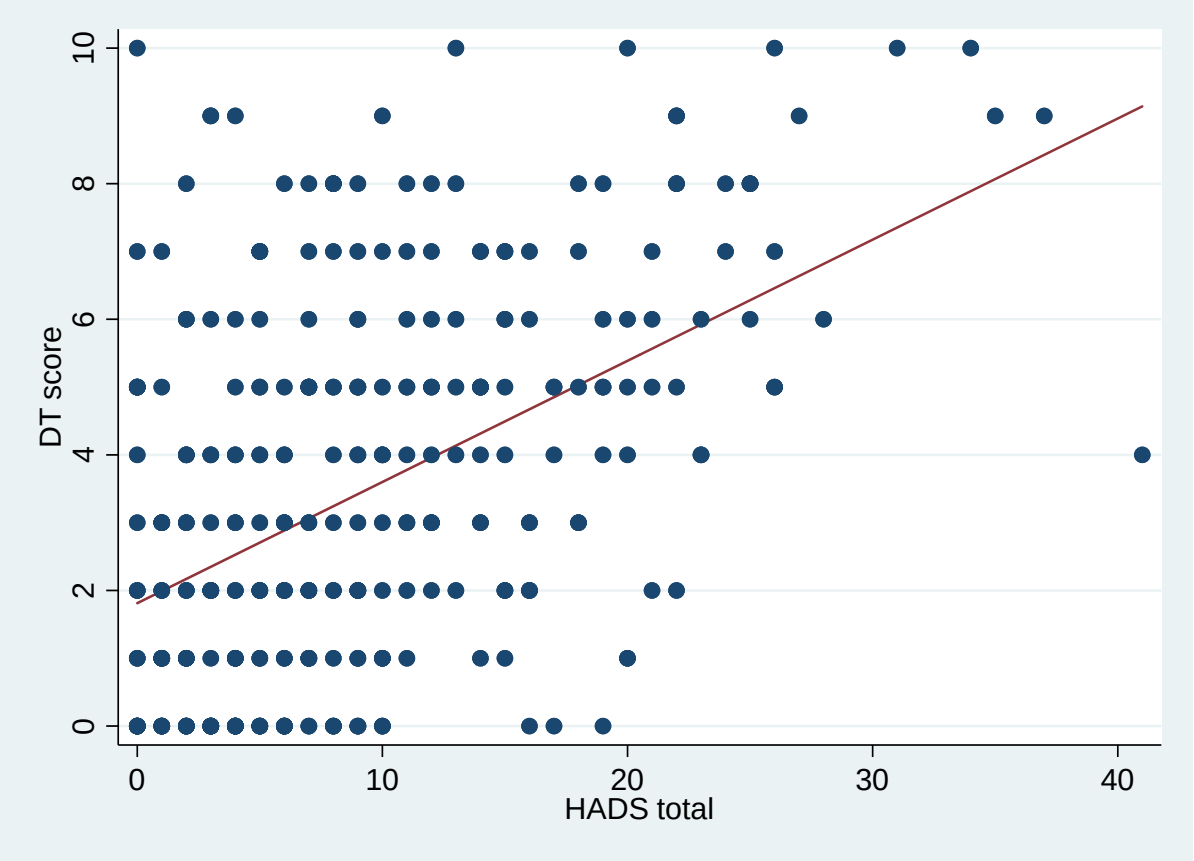


6.4.4 Construct Validity of the DT

Relationship between Distress and depression – comparison of DT and HADS scores

Figure 6.15 shows the association between DT scores and total HADS scores. While overall correlation is good (Spearman's rho is 0.450), there are outliers with high DT scores but low HADS scores (and vice versa) suggesting that not all highly distressed participants would meet the criteria for depression or anxiety on the HADS.

Figure 6.15 Linear regression showing Distress Thermometer scores against HADS scores. Spearman's rho 0.450

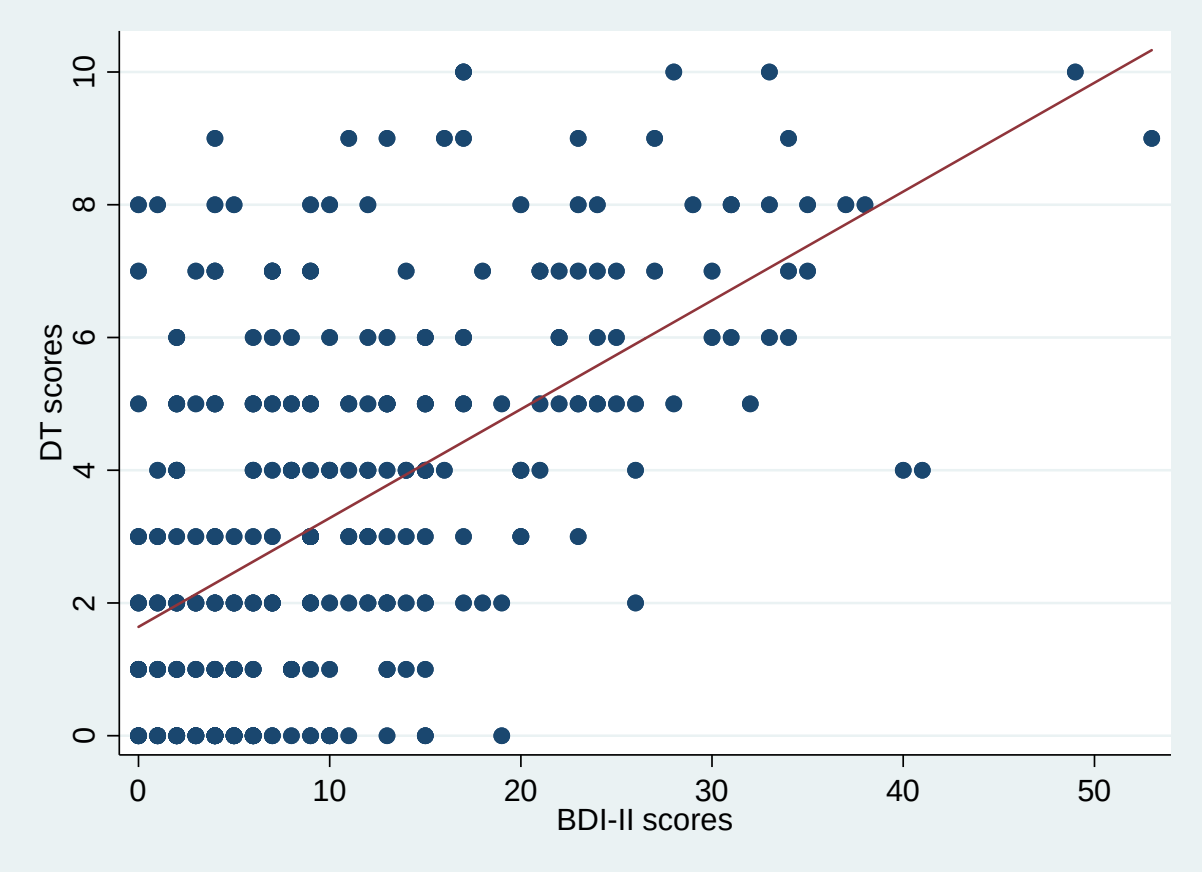


Relationship between Distress and depression – comparison of DT and BDI-II scores

Similarly, **Error! Not a valid bookmark self-reference.** shows good correlation between DT scores and the BDI-II.

Figure 6.16 Linear regression of Distress Thermometer scores against BDI-II scores

Spearman's rho 0.530

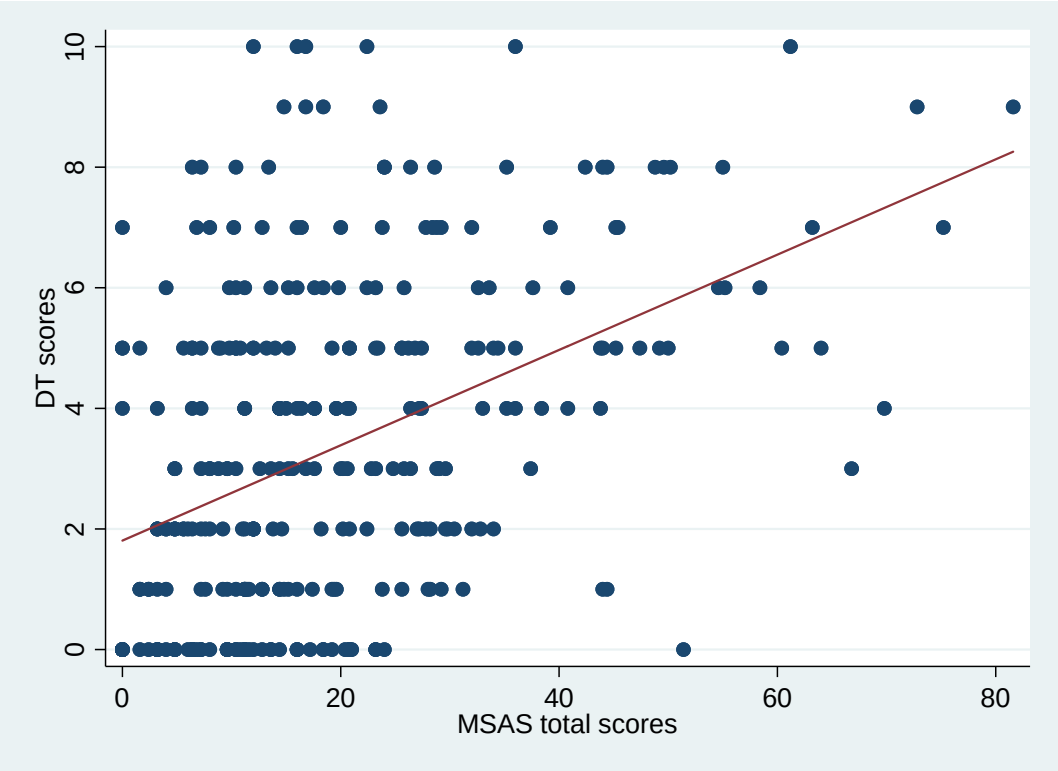


Relationship between Distress and symptom burden – comparison of DT and MSAS-SF scores

Figure 6.17 shows a positive correlation between DT scores and increased symptoms on the MSAS-SF. Spearman's rho is 0.438, suggesting moderately good correlation, however there are a substantial number of participants who score 10 on the DT (maximum levels of distress) but do not score highly on the MSAS.

Figure 6.17 Linear regression of DT scores against MSAS total scores

Spearman's rho 0.438



Relationship between Distress and Quality of Life – comparison of DT and SF-36 subscales

Error! Reference source not found.18 shows a negative relationship between DT scores and the SF 3 6 Physical Functioning subscale. This is to be expected, as higher SF 36 scores indicate better physical function. Spearman's rho is only -0.271, suggesting a very loose correlation. The associations between DT score and Physical Role (**Error! Reference source not found.**) and DT and Emotional Role (Figure 6.20) are similarly loose.

There is a much stronger association between DT score and the Energy subscale (Figure 6.21), although there are still many participants with low energy who are not distressed, and those with good energy levels but high levels of distress.

The association between DT score and Emotional Wellbeing subscale (Figure 6.22) is also strong – this is to be expected, as Emotional Wellbeing is an extremely similar concept to that of Distress.

The associations between DT scores and the SF-36 Social Functioning (Figure 6.23), Pain (Figure 6.24) and General Health (Figure 6.25) subscales are less strong, with several outliers in both directions indicating that distress is due to more than simply poor physical health, and that it is possible to have poor general health or high levels of pain without these problems causing distress.

Figure 6.18 Linear regression of Distress Thermometer scores against SF-36 Physical Functioning subscale

Spearman's rho -0.271

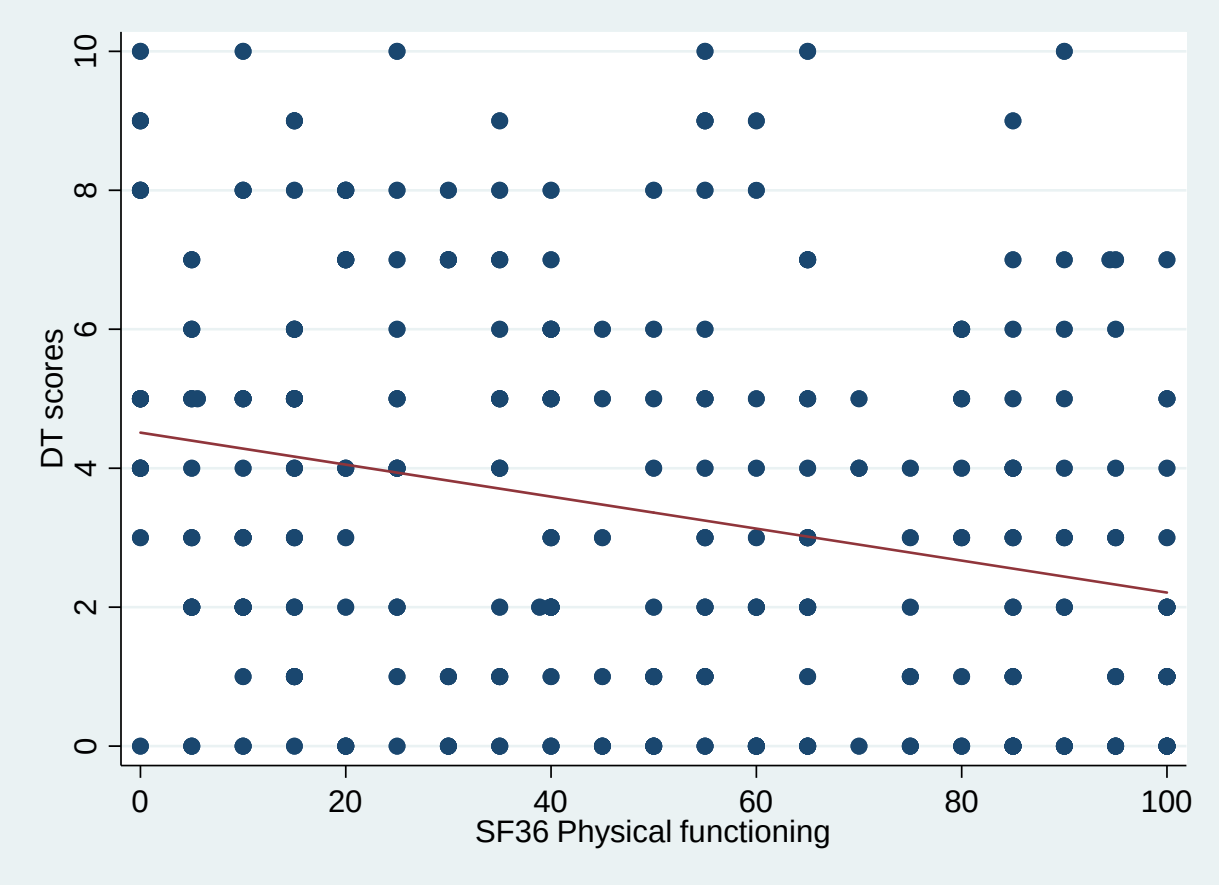


Figure 6.19 Linear regression of Distress Thermometer scores against SF-36 Physical Role subscale

Spearman's rho -0.230

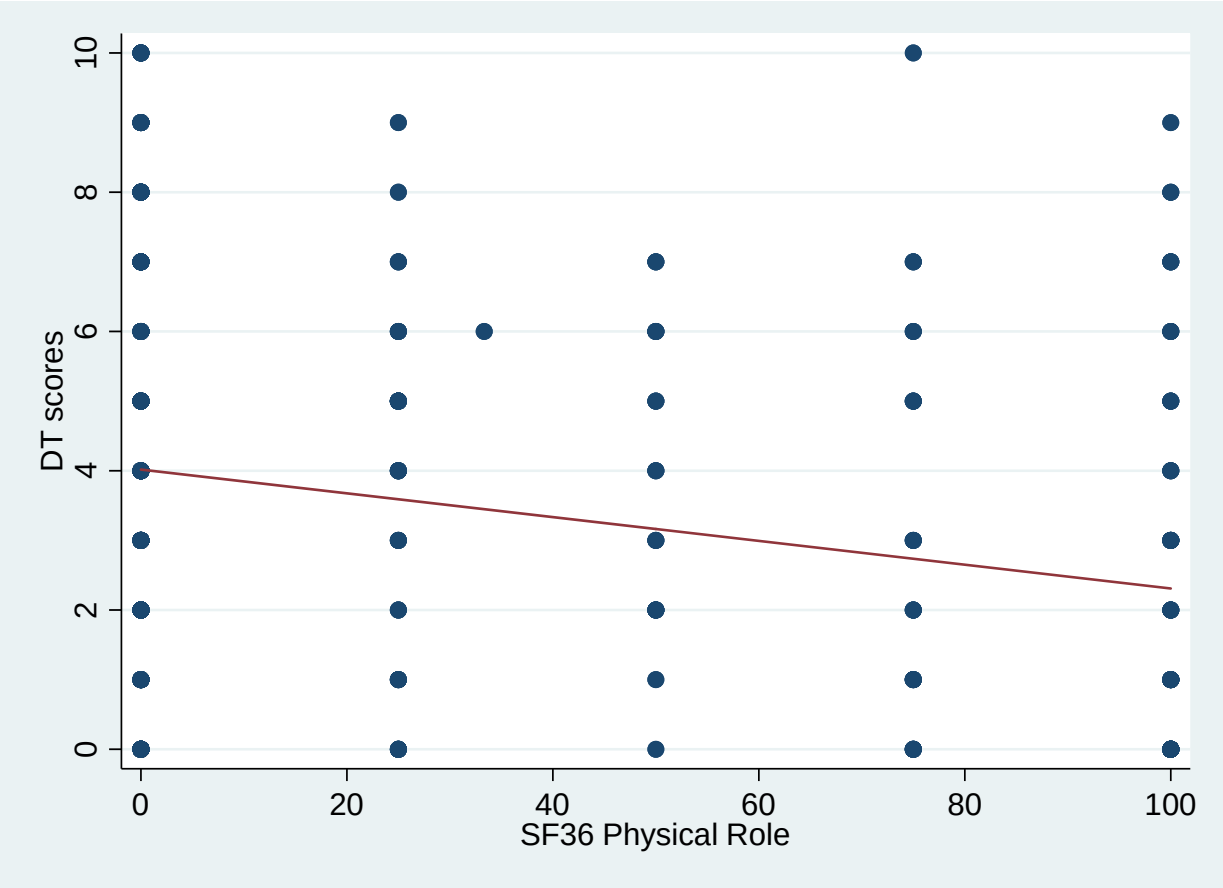


Figure 6.20 Linear regression of Distress Thermometer scores against SF-36 Emotional Role subscale

Spearman's rho -0.211

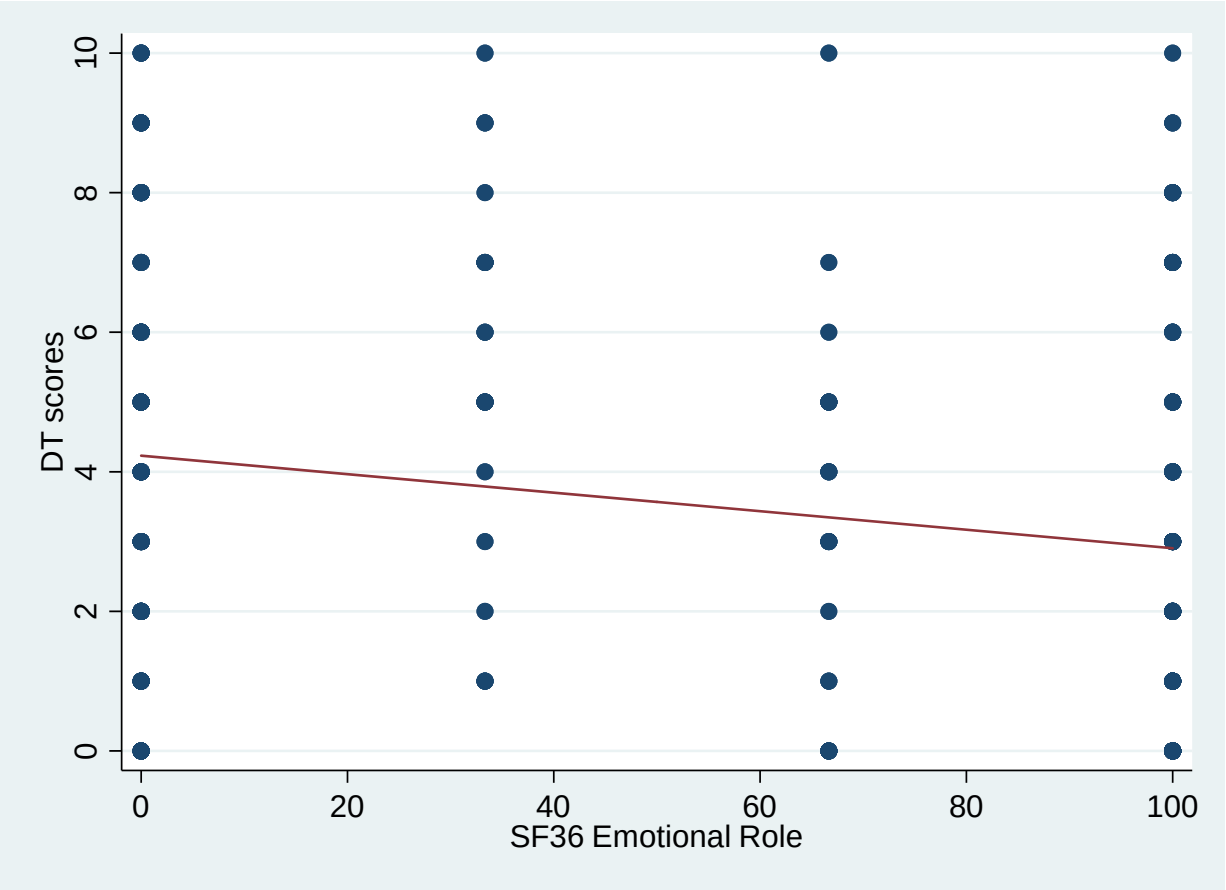


Figure 6.21 Linear regression of Distress Thermometer scores against SF-36 Energy subscale Spearman's rho -0.409

Figure 6.22 Linear regression of Distress Thermometer scores against SF-36 Emotional Wellbeing subscale

Spearman's rho -0.488

Figure 6.23 Linear regression of Distress Thermometer scores against SF-36 Social Functioning subscale

Spearman's rho -0.381

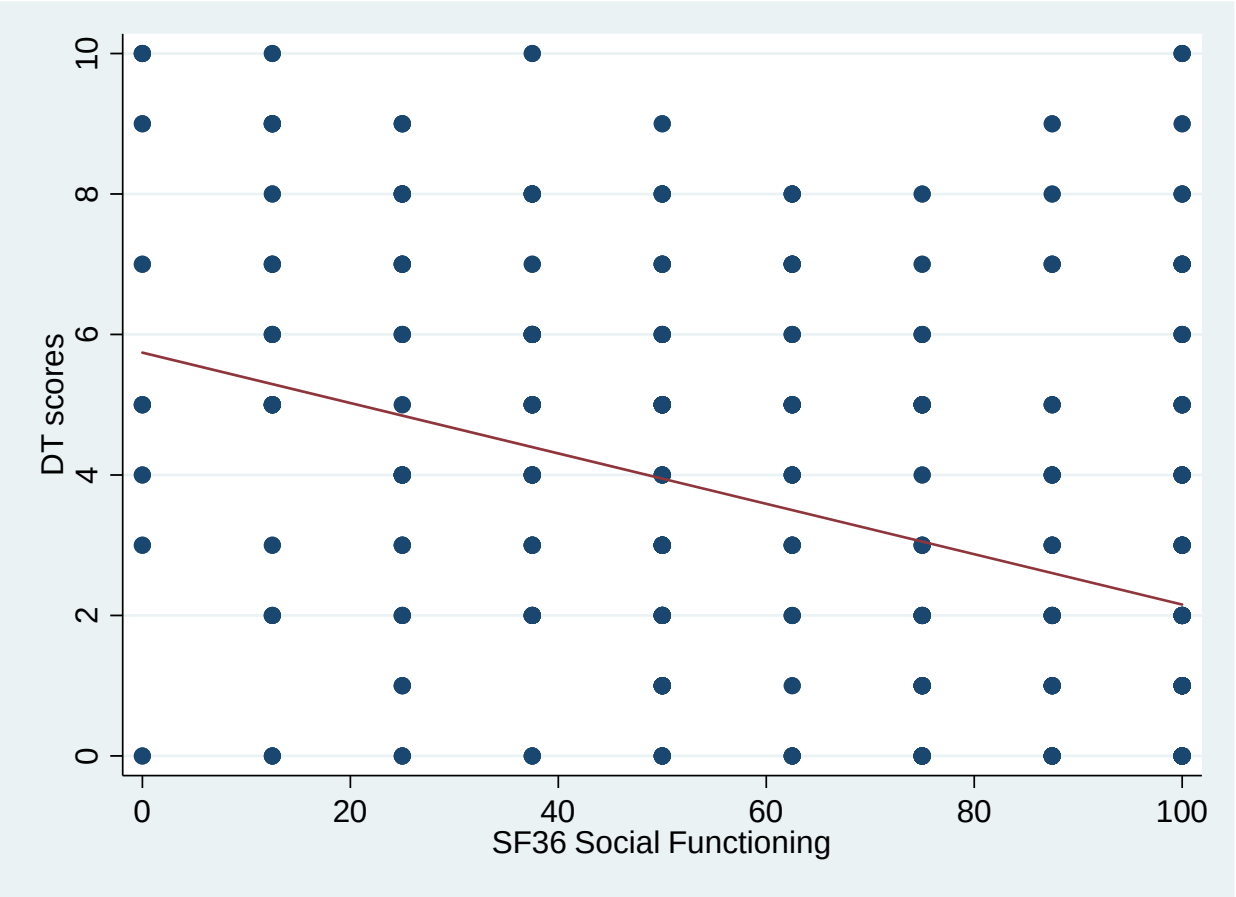


Figure 6.24 Linear regression of Distress Thermometer scores against SF-36 Pain subscale

Spearman's rho -0.298

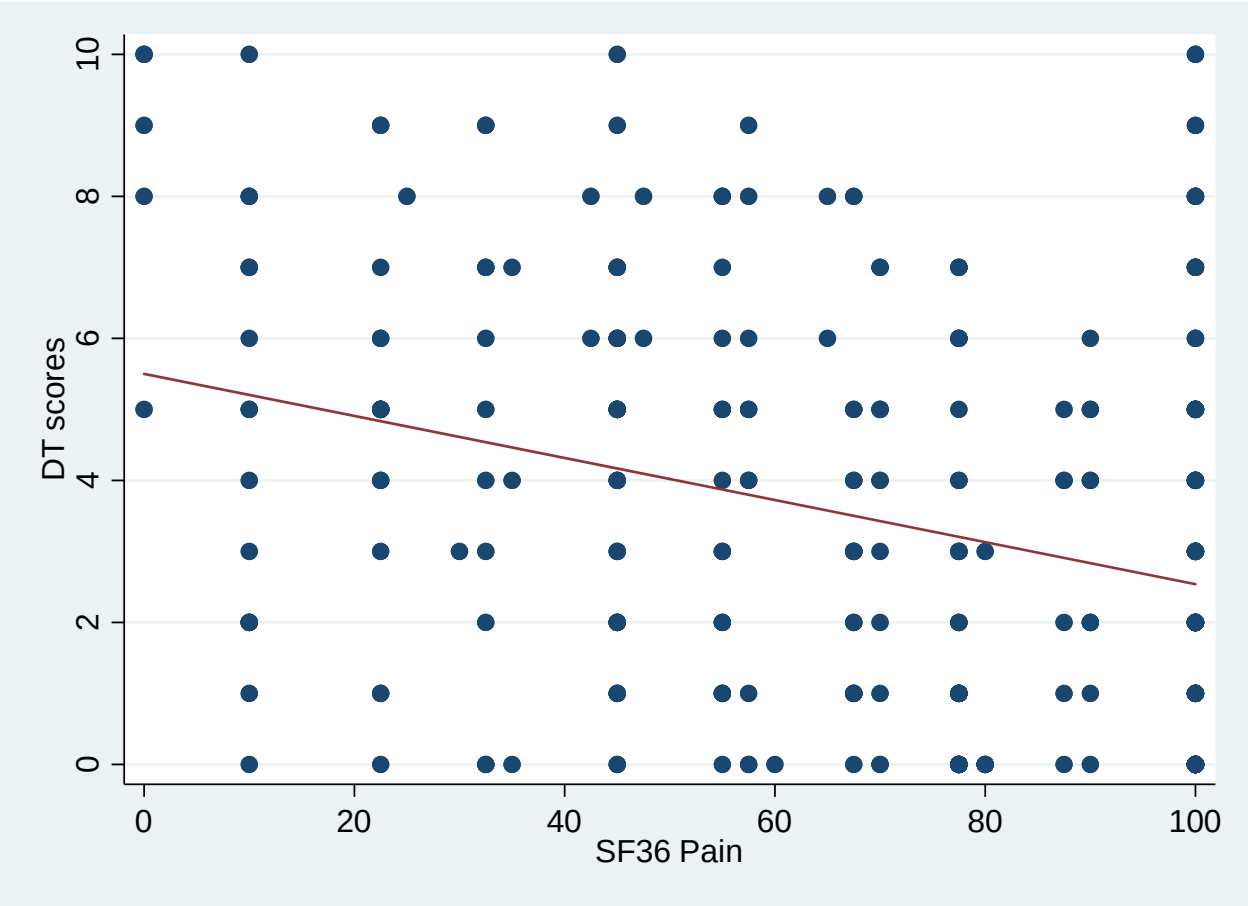
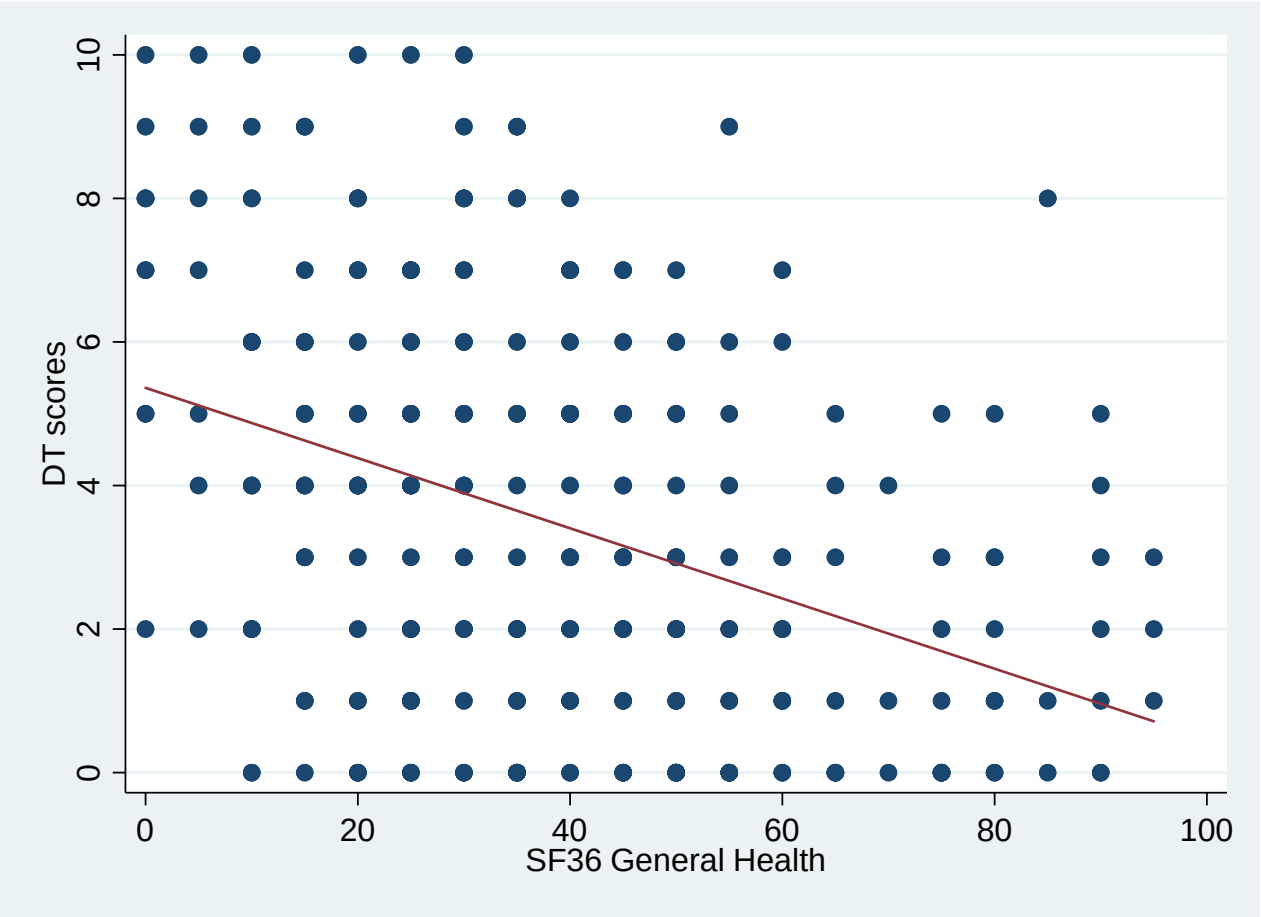


Figure 6.25 Linear regression of Distress Thermometer scores against SF-36 General Health subscale

Spearman's rho -0.384



6.4.5 Identification of "cut-off" threshold for the Distress Thermometer

ROC curve analysis was performed to examine the sensitivity and specificity of different DT scores against the cut-off scores used to identify patients with a high likelihood of depression ('caseness') on the HADS and BDI-II questionnaires.

Figure 6.26 shows the ROC curve for DT versus HADS. The area under the curve AUC is 0.76 (95% confidence interval 0.70-0.82, $p < 0.001$). An AUC > 0.70 is accepted as a strong association in studies of psychological tests (as there may be many other factors which introduce variation in the results of these tests)[310].

Figure 6.26 Receiver operator characteristic curve for Distress Thermometer scores plotted against HADS cases

AUC 0.76 (CI 0.70-0.82, $p < 0.001$)

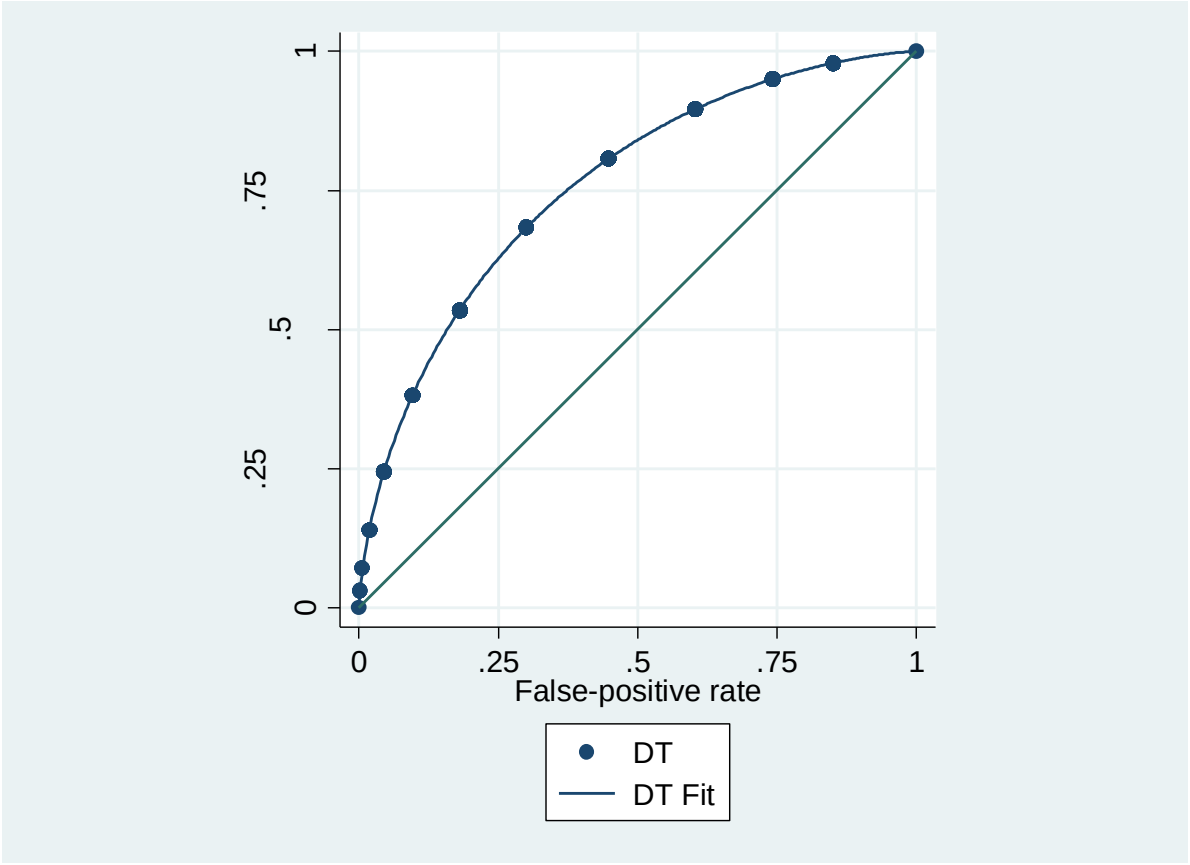


Figure 6.27 Receiver operator characteristic curve for Distress Thermometer scores against BDI-II scores

AUC 0.87 (CI 0.83-0.92, p < 0.001)

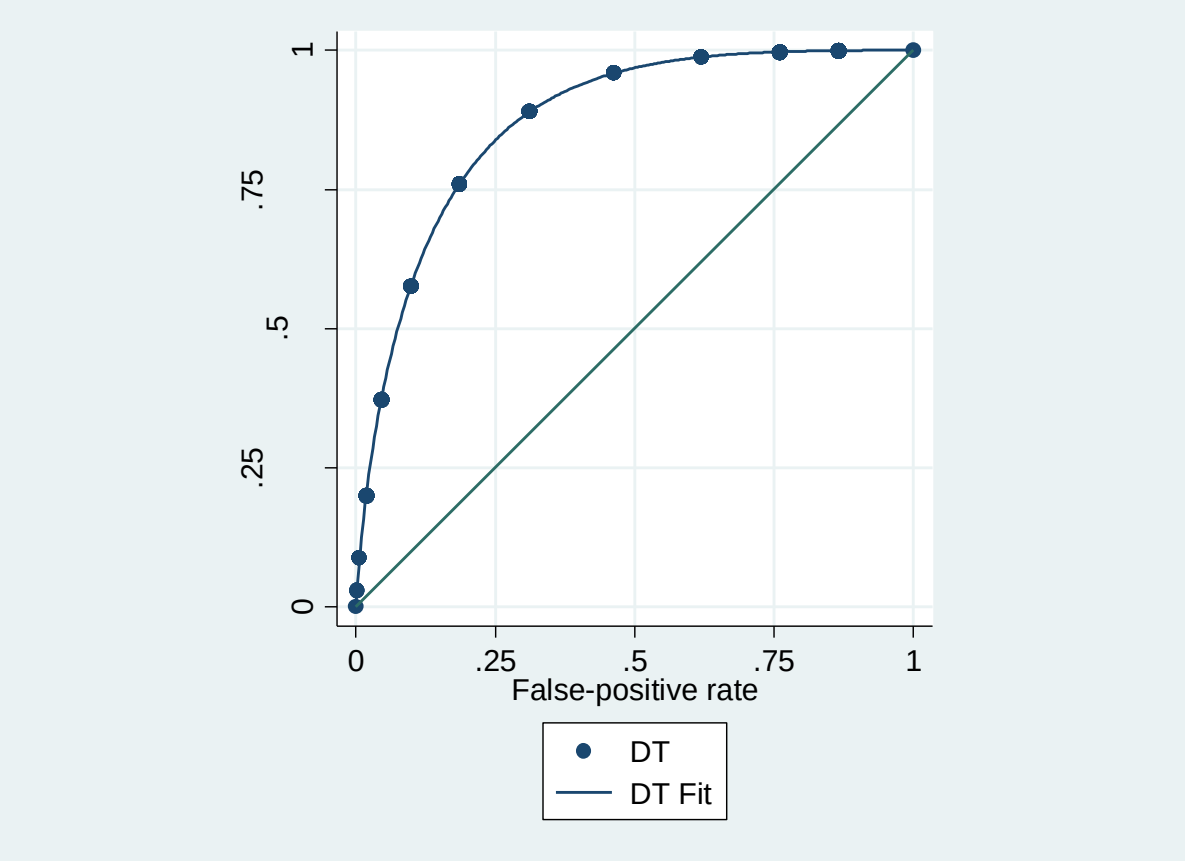


Figure 6.27 shows the ROC curve for DT versus BDI-II. The AUC is 0.86 (95% CI 0.83-0.92, p < 0.001). This shows a strong association between BDI cases and DT scores.

We then tabulated the different sensitivities and specificities of different DT 'cut-off' scores in detecting 'caseness' for the HADS and BDI-II (Table 6.4). The precise cut-off to use would depend on whether the DT was being used as a screening tool (in which case a high sensitivity is important, and false positives can be excluded at a later date), or whether the aim is to use the DT as a diagnostic tool, in which case a balance between false positives and negatives needs to be achieved.

Table 6.4 Sensitivity and specificity of different cut-off points to describe 'caseness' for distress using Distress Thermometer

	DT cut off ≥5	DT cut off ≥6	DT cut off ≥7
HADS	PPV = 49.5% NPV = 82.3% Sens = 60.2% Spec = 75.1%	PPV = 53.7% NPV = 78.1% Sens = 40.9% Spec = 75.3%	PPV = 53.2% NPV = 75.6% Sens = 28.4% Spec = 89.9%
BDI	PPV = 39.4% NPV = 94.8% Sens = 80.4% Spec = 74.5%	PPV = 49.2% NPV = 91.8% Sens = 62.7% Spec = 86.6%	PPV = 53.3% NPV = 89.3% Sens = 47.1% Spec = 91.5%

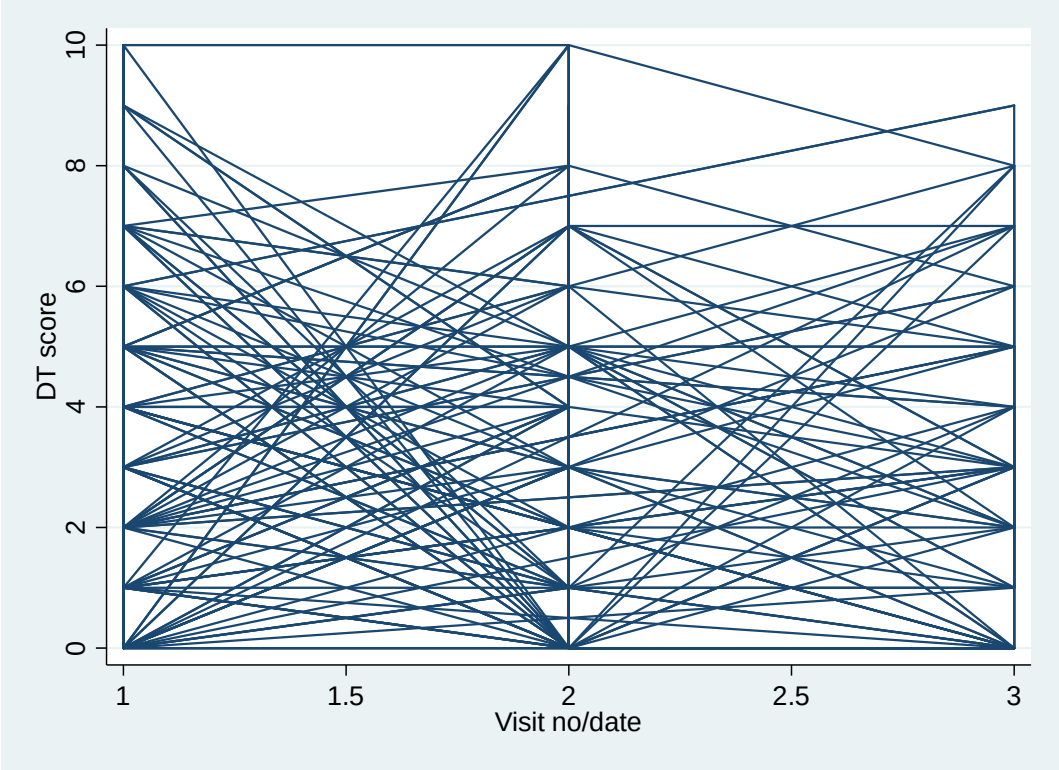
6.4.6 Sensitivity to change over time

Change in DT scores over time

Figure 6.28 shows the trajectory of DT scores over the three visits, for each participant. It is clear that for some participants, DT scores vary significantly from visit to visit.

Linear regression of DT by visit number was performed. This showed a co-efficient of -0.33, suggesting that DT scores declined by 0.33 points at each subsequent visit. However it is clear from the plot of the trajectories that in fact some participants' scores went up and some went down. Indeed, confidence intervals approach 0 (-0.63 - -0.03) and p= 0.033. The full Stata output is shown on the next page.

Figure 6.28 Trajectories of DT scores of time



Linear regression

```
. regress dt visitnodate

      Source |       SS       df       MS      Number of obs   =       600
-------------+------------------------------   F(1, 598)       =      4.58
       Model |  36.4116214     1  36.4116214   Prob > F        =    0.0327
    Residual |  4751.57338   598  7.94577488   R-squared       =    0.0076
-------------+------------------------------   Adj R-squared   =    0.0059
       Total |   4787.985    599  7.99329716   Root MSE        =    2.8188

------------------------------------------------------------------------------
          dt |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 visitnodate |  -.3297855   .1540564    -2.14   0.033    -.6323429   -.0272282
       _cons |   3.794749   .2771588    13.69   0.000     3.250426    4.339072
------------------------------------------------------------------------------
```

We then carried out a mixed effects regression. First we carried out a random intercept mixed effects regression (shown below, Model M1), and compared this with a random slope, random intercept model (shown on following pages, Model M2). Likelihood-ratio testing was non-significant (p=0.102), suggesting that the random slope, random intercept model was no better than Model M1. This is not surprising, as the likelihood statistics are very similar between both models and the confidence intervals of the level 1 residuals overlap. Model 2 was therefore discarded.

The interpretation of this model is that, although different participants have different starting levels of distress (random intercept), the trajectories over time are very similar (so the random slope model offers no better fit than the fixed slope model).

Intraclass correlation coefficient was calculated as 0.497 (95% CI 0.410 - 0.585), suggesting that 49.7% of the variation in DT scores is due to differences between individuals. Cicchetti (1994)[318] suggested that this represented merely “fair” reliability (with ICCs > 0.60 representing “good” reliability).

Model M1

```
. mixed dt visitnodate || hospitalnumber:

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -1427.0521
Iteration 1:   log likelihood = -1427.0507
Iteration 2:   log likelihood = -1427.0507

Computing standard errors:

Mixed-effects ML regression                 Number of obs     =       600
Group variable: hospitalnumber              Number of groups  =       323

                                            Obs per group:
                                                          min =         1
                                                          avg =       1.9
                                                          max =         3

                                            Wald chi2(1)      =      8.41
Log likelihood = -1427.0507                 Prob > chi2       =    0.0037

------------------------------------------------------------------------------
          dt |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 visitnodate |  -.3509514   .1210502    -2.90   0.004    -.5882054   -.1136975
       _cons |   3.817636   .2318943    16.46   0.000     3.363132    4.272141
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
hospitalnu~r: Identity       |
```

```
              var(_cons) |   3.935316   .5278177      3.025615    5.118535
-----------------------------+------------------------------------------------
           var(Residual) |   3.977309   .3314825      3.377904    4.683078
------------------------------------------------------------------------------
LR test vs. linear model: chibar2(01) = 90.21        Prob >= chibar2 = 0.0000

. estimate store m1

. estat icc

Residual intraclass correlation

------------------------------------------------------------------------------
                  Level |       ICC   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
          hospitalnumber |   .4973465   .0452906      .4095815    .5852753
------------------------------------------------------------------------------
```

Model M2

```
. mixed dt visitnodate || hospitalnumber: visitnodate, cov(unst)

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -1425.7479
Iteration 1:   log likelihood =  -1424.766
Iteration 2:   log likelihood =  -1424.765
Iteration 3:   log likelihood =  -1424.765

Computing standard errors:

Mixed-effects ML regression                 Number of obs     =        600
Group variable: hospitalnumber              Number of groups  =        323
```

```
                                        Obs per group:
                                                      min =         1
                                                      avg =       1.9
                                                      max =         3

                                        Wald chi2(1)      =      7.66
Log likelihood =  -1424.765             Prob > chi2       =    0.0057

------------------------------------------------------------------------------
          dt |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 visitnodate |  -.3546641   .1281737    -2.77   0.006     -.60588   -.1034482
       _cons |   3.821944   .2440344    15.66   0.000     3.343645    4.300242
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
hospitalnu~r: Unstructured   |
             var(visitn~e) |    .769395    .388454      .2860175    2.069694
               var(_cons) |   7.280995   1.751983      4.543298    11.66837
        cov(visitn~e,_cons) |  -1.578982    .773188     -3.094402   -.0635612
-----------------------------+------------------------------------------------
             var(Residual) |   3.292471   .3934846       2.60492    4.161495
------------------------------------------------------------------------------
LR test vs. linear model: chi2(3) = 94.78                 Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.

. estimate store m2

. estat icc

Conditional intraclass correlation
```

```
------------------------------------------------------------------------------
                Level |       ICC   Std. Err.     [95% Conf. Interval]
----------------------+-------------------------------------------------------
       hospitalnumber |   .6886101   .0694749      .5395654    .8066933
------------------------------------------------------------------------------
```

Note: ICC is conditional on zero values of random-effects covariates.

Likelihood-ratio test of M1 vs M2

. lrtest m2 m1

Likelihood-ratio test LR chi2(2) = 4.57

(Assumption: m1 nested in m2) Prob > chi2 = 0.1017

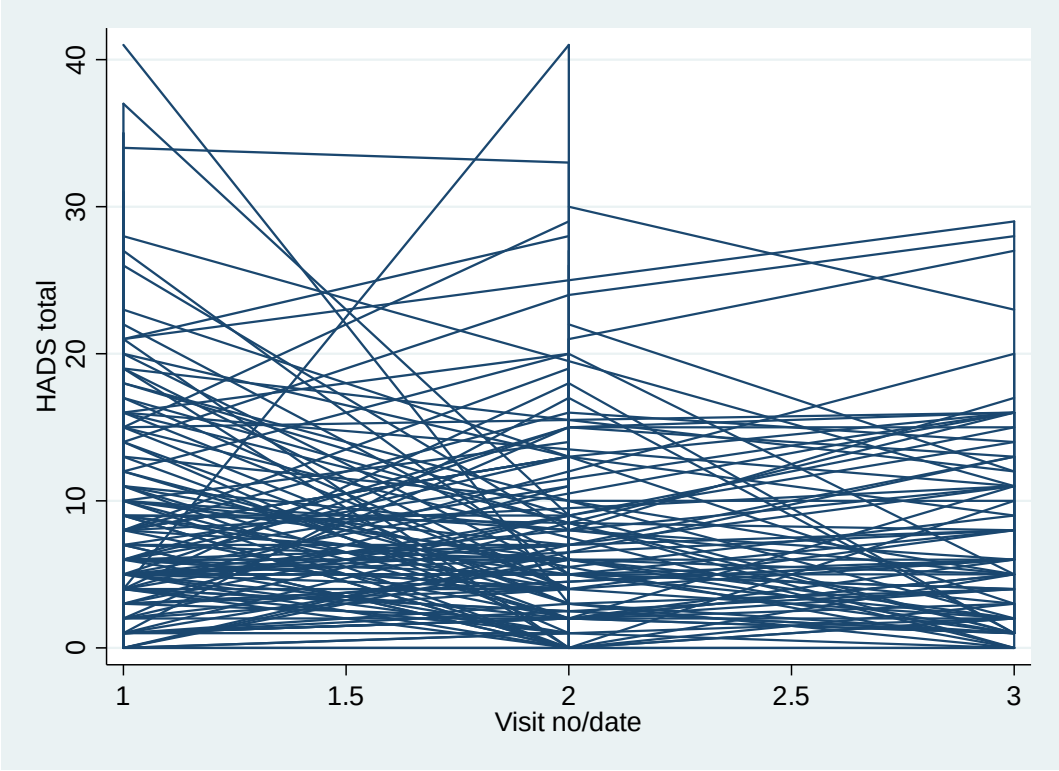
Note: The reported degrees of freedom assumes the null hypothesis is not on the boundary of the parameter space. If this is not true, then the reported test is conservative.

Change in HADS scores over time

Figure 6.29 shows how HADS scores changed for each participant across the three visits. Although some participants do demonstrate high variability from visit to visit, the overall trend is much less erratic. Linear regression suggests that, for each clinic visit, the HADS score declines by 1.026 points (95% CI -1.825 - -0.227, p = 0.012).

We also created a mixed level model (Model 3) in order to compare the ICC with that of the DT (we created a fixed slope random intercept model only, in order to directly compare with the best-fitting model for the DT). The ICC was 0.717 (95% CI 0.657 - 0.770), suggesting that 71.7% of the variability was due to differences between individuals ("good reliability"[318]).

Figure 6.29 Trajectories of HADS scores of time



Linear regression

```
. regress hadstotal visitnodate

      Source |       SS       df       MS      Number of obs   =       609
-------------+------------------------------   F(1, 607)       =      6.35
       Model |  357.766483         1  357.766483   Prob > F        =    0.0120
    Residual |  34175.8591       607  56.3028981   R-squared       =    0.0104
-------------+------------------------------   Adj R-squared   =    0.0087
       Total |  34533.6256       608  56.7987263   Root MSE        =    7.5035

------------------------------------------------------------------------------
  hadstotal |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
visitnodate |  -1.025988   .4070125    -2.52   0.012    -1.825311   -.2266641
      _cons |    10.1409    .729989    13.89   0.000     8.707286    11.57451
------------------------------------------------------------------------------
```

Model M3

```
. mixed hadstotal visitnodate || hospitalnumber:

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -1979.5525
Iteration 1:   log likelihood = -1979.5525

Computing standard errors:

Mixed-effects ML regression                 Number of obs     =       609
Group variable: hospitalnumber              Number of groups  =       326

                                            Obs per group:
                                                          min =         1
                                                          avg =       1.9
```

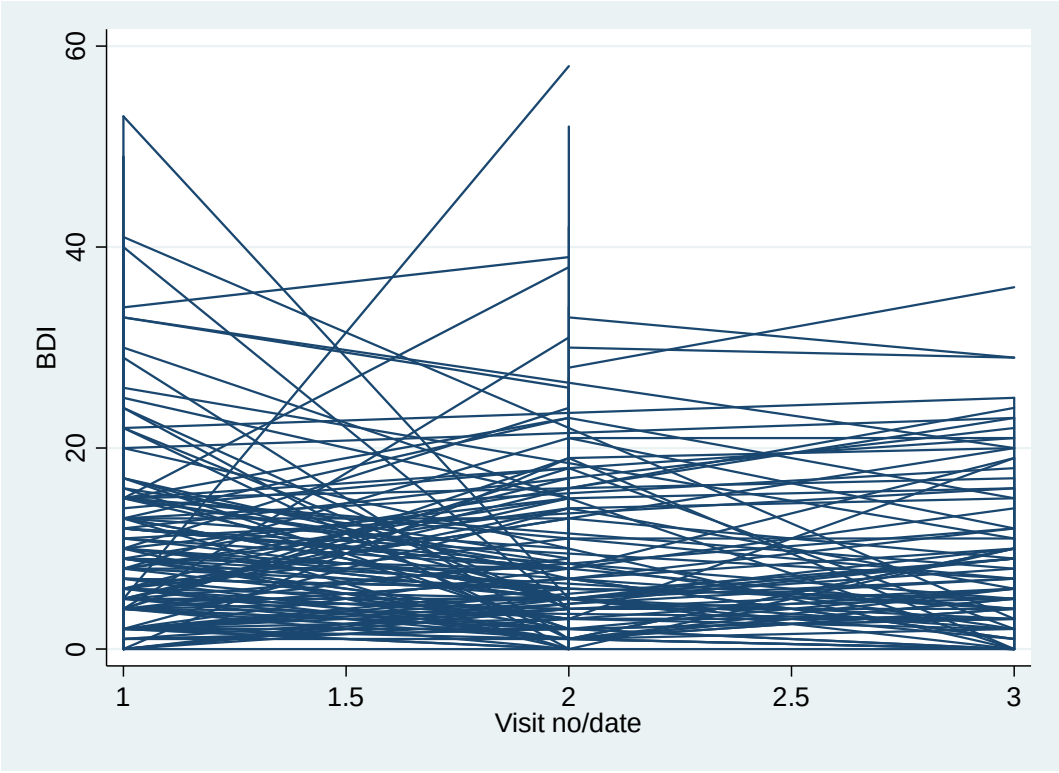
```
                                                max =         3

                                        Wald chi2(1)     =      20.34
Log likelihood = -1979.5525             Prob > chi2      =     0.0000

------------------------------------------------------------------------------
  hadstotal |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
visitnodate |  -1.116413   .2475333    -4.51   0.000     -1.60157    -.631257
      _cons |   10.22053   .5375679    19.01   0.000     9.166912    11.27414
------------------------------------------------------------------------------

------------------------------------------------------------------------------
 Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
----------------------------+-------------------------------------------------
hospitalnu~r: Identity      |
              var(_cons) |   40.34112   4.022251      33.18013    49.04761
----------------------------+-------------------------------------------------
           var(Residual) |   15.90281   1.330528      13.49761    18.73659
------------------------------------------------------------------------------
LR test vs. linear model: chibar2(01) = 221.88        Prob >= chibar2 = 0.0000

.
. estat icc

Residual intraclass correlation

------------------------------------------------------------------------------
                 Level |        ICC   Std. Err.     [95% Conf. Interval]
-----------------------+------------------------------------------------------
          hospitalnumber |   .7172529   .0289094      .6573443    .7703466
------------------------------------------------------------------------------
```

Change in BDI-II scores over time

Figure 6.30 shows how BDI-II scores changed for each participant across the three visits. Again, despite some outliers the overall trend is much less erratic than that of the DT. Linear regression suggests that, for each clinic visit, the BDI-II score declines (ie depression improves) by 1.151 points (95% CI -2.160 - -0.141, p = 0.026).

We created a fixed slope random intercept mixed level model (Model 4) in order to compare the ICC for the BDI-II with that of the DT. The ICC was 0.740 (95% CI 0.683 – 0.790), suggesting that 74% of the variability was due to differences between individuals ("excellent reliability"[318]).

Figure 6.30 Trajectories of BDI-II scores of time



Linear regression

```
. regress bdi visitnodate

      Source |       SS       df       MS      Number of obs   =       597
-------------+------------------------------   F(1, 595)       =      5.01
       Model |  445.171785     1  445.171785   Prob > F        =    0.0255
    Residual |  52843.2805   595  88.8122361   R-squared       =    0.0084
-------------+------------------------------   Adj R-squared   =    0.0067
       Total |  53288.4523   596  89.4101548   Root MSE        =     9.424

------------------------------------------------------------------------------
         bdi |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 visitnodate |  -1.150838   .5140279    -2.24   0.026    -2.160367    -.141308
       _cons |   11.94869   .9254224    12.91   0.000     10.1312    13.76618
------------------------------------------------------------------------------
```

Model M4

```
. mixed bdi visitnodate || hospitalnumber:

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -2071.6093
Iteration 1:   log likelihood = -2071.6093

Computing standard errors:

Mixed-effects ML regression                     Number of obs     =        597
Group variable: hospitalnumber                  Number of groups  =        320

                                                Obs per group:
                                                              min =          1
                                                              avg =        1.9
```

```
                                                max =         3

                                        Wald chi2(1)     =     12.23
Log likelihood = -2071.6093             Prob > chi2      =     0.0005

------------------------------------------------------------------------------
         bdi |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 visitnodate |  -1.059934   .3030403    -3.50   0.000    -1.653882   -.4659857
       _cons |   11.84257   .6766535    17.50   0.000     10.51635    13.16878
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
hospitalnu~r: Identity       |
                var(_cons) |   66.85792   6.618083      55.06742    81.17288
-----------------------------+------------------------------------------------
             var(Residual) |   23.44717   1.996054      19.84393    27.70467
------------------------------------------------------------------------------
LR test vs. linear model: chibar2(01) = 227.45        Prob >= chibar2 = 0.0000

. estat icc

Residual intraclass correlation

------------------------------------------------------------------------------
                  Level |       ICC   Std. Err.     [95% Conf. Interval]
------------------------+-----------------------------------------------------
           hospitalnumber |   .7403561   .0274364      .6831051     .790437
------------------------------------------------------------------------------
```

Changes in relationship between DT and HADS over time

We then assessed the stability of the relationship between DT score and HADS score over the three visits by fitting a fixed slope random intercept mixed level model (Model 5) and a random slope random intercept mixed level model (Model 6). Both models fit the data better than a linear model ($p < 0.001$), however likelihood ratio test suggested that Model 5 was nested within Model 6 ($p = 0.023$), so we rejected Model 5. The random slope and random intercept of Model 6 suggest that different participants not only have different starting levels of distress, but also that the relationship between DT and HADS changes across the three clinic visits.

Model 6 suggests that, for each one-point increase in HADS score, DT score increases by 0.188 points when adjusted for clinic visit (95% CI 0.161 – 0.216, $p < 0.001$). At each subsequent clinic visit, DT score improves by -0.140 adjusted for HADS score (although 95% CI -0.384 – 0.103, $p = 0.258$).

ICC was estimated at 0.646 (95% CI 0.476 – 0.785), suggesting that approximately 64.6% of variation in the relationship between HADS and DT is due to individual differences between participants.

Model 5

```
. mixed dt hadstotal visitnodate || hospitalnumber:

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -1357.8252
Iteration 1:   log likelihood = -1357.7079
Iteration 2:   log likelihood = -1357.7079

Computing standard errors:
```

```
Mixed-effects ML regression                 Number of obs     =        600
Group variable: hospitalnumber              Number of groups  =        323

                                            Obs per group:
                                                          min =          1
                                                          avg =        1.9
                                                          max =          3

                                            Wald chi2(2)      =     188.42
Log likelihood = -1357.7079                 Prob > chi2       =     0.0000

------------------------------------------------------------------------------
          dt |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  hadstotal |   .1868887   .0139425    13.40   0.000     .1595619    .2142155
visitnodate |  -.1426847   .1186484    -1.20   0.229    -.3752312    .0898619
      _cons |   1.898811   .2581588     7.36   0.000     1.392829    2.404792
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
hospitalnu~r: Identity       |
                  var(_cons) |   1.594601   .3521285      1.034391     2.45821
-----------------------------+------------------------------------------------
               var(Residual) |   4.067111   .3345184      3.461585     4.77856
------------------------------------------------------------------------------
LR test vs. linear model: chibar2(01) = 27.23        Prob >= chibar2 = 0.0000

. estimate store m5
```

Model M6

```
. mixed dt hadstotal visitnodate || hospitalnumber: visitnodate, cov(unst)

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log likelihood =  -1355.058
Iteration 1:   log likelihood = -1353.9145
Iteration 2:   log likelihood = -1353.9136
Iteration 3:   log likelihood = -1353.9136

Computing standard errors:

Mixed-effects ML regression                 Number of obs     =        600
Group variable: hospitalnumber              Number of groups  =        323

                                            Obs per group:
                                                          min =          1
                                                          avg =        1.9
                                                          max =          3

                                            Wald chi2(2)      =     192.79
Log likelihood = -1353.9136                 Prob > chi2       =     0.0000

------------------------------------------------------------------------------
          dt |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  hadstotal |   .1883787   .0138578    13.59   0.000      .161218    .2155394
visitnodate |  -.1404105   .1241613    -1.13   0.258    -.3837622    .1029411
      _cons |   1.883064   .2706124     6.96   0.000     1.352674    2.413455
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
```

```
------------------------------+------------------------------------------------
hospitalnu~r: Unstructured    |
           var(visitn~e) |   .8942682   .3743239      .3937049    2.031257
             var(_cons) |   5.881687    1.60509      3.445182    10.04134
       cov(visitn~e,_cons) |  -1.942568   .7398941    -3.392734    -.492402
------------------------------+------------------------------------------------
           var(Residual) |   3.226515   .3735847      2.571442    4.048468
------------------------------------------------------------------------------
LR test vs. linear model: chi2(3) = 34.82                 Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.

. estimate store m6

. estat icc

Conditional intraclass correlation

------------------------------------------------------------------------------
                Level |        ICC   Std. Err.     [95% Conf. Interval]
------------------------------+-----------------------------------------------
           hospitalnumber |   .6457572   .0811096      .4763918    .7850572
------------------------------------------------------------------------------
Note: ICC is conditional on zero values of random-effects covariates.

. lrtest m6 m5

Likelihood-ratio test                         LR chi2(2)  =      7.59
(Assumption: m5 nested in m6)                 Prob > chi2 =    0.0225

Note: The reported degrees of freedom assumes the null hypothesis is not on the boundary of the
parameter space.  If this is not true, then the reported test is conservative.
```

Changes in relationship between DT and BDI-II over time

To assess the stability of the relationship between DT score and BDI-II scores over the three visits, we fitted a fixed slope random intercept mixed level model (Model 7) and a random slope random intercept mixed level model (Model 8). Both models fit the data better than a linear model ($p < 0.001$), however the likelihood ratio test hypothesising that Model 7 was nested within Model 8 was non-significant ($p = 0.072$), so we rejected Model 8.

This implies that, while participants have different starting levels of distress (random intercepts), the trajectory of the relationship between DT and BDI-II across the three clinic visits are not significantly different (so the random slope model provides no better fit than the fixed slope model). As previously established in Section **Error! Reference source not found.**, BDI-II scores are very closely c orrelated with DT scores (AUC 0.87). We saw on p101 that different participants have similar trajectories of distress across the three clinic visits despite different starting levels of distress, so it should be no surprise that the relationship between DT and BDI-II scores is also stable over time.

Model 7 suggests that, for each one-point increase in BDI-II score, DT score increases by 0.165 points when adjusted for clinic visit (95% CI 0.145 – 0.186, $p < 0.001$). At each subsequent clinic visit, DT score improves by -0.140 adjusted for BDI-II score (although this was non-significant; 95% CI -0.368 – 0.088, $p = 0.228$).

ICC was estimated at 0.222 (95% CI 0.133 – 0.346), suggesting that only 22.2% of variation in the relationship between DT and BDI-II is due to individual differences between participants – this is quite a lot lower than the effect of clustering on DT scores and BDI-II scores themselves, and does suggest that another unidentified major factor influences the relationship between the DT and BDI-II.

Model M7

```
. mixed dt bdi visitnodate || hospitalnumber:

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -1306.7972
Iteration 1:   log likelihood = -1306.5633
Iteration 2:   log likelihood = -1306.5633

Computing standard errors:

Mixed-effects ML regression                 Number of obs     =        588
Group variable: hospitalnumber              Number of groups  =        317

                                            Obs per group:
                                                          min =          1
                                                          avg =        1.9
                                                          max =          3

                                            Wald chi2(2)      =     253.56
Log likelihood = -1306.5633                 Prob > chi2       =     0.0000

------------------------------------------------------------------------------
          dt |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         bdi |   .1652745   .0105571    15.66   0.000     .1445831     .185966
 visitnodate |  -.1402356   .1164005    -1.20   0.228    -.3683764    .0879052
       _cons |   1.781875   .2464766     7.23   0.000      1.29879     2.26496
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
```

```
hospitalnu~r: Identity       |
             var(_cons) |   1.137839   .3021018      .6762114    1.914604
----------------------------+----------------------------------------------
          var(Residual) |   3.990512   .3227552      3.405516    4.675999
------------------------------------------------------------------------------
LR test vs. linear model: chibar2(01) = 17.95        Prob >= chibar2 = 0.0000
```

```
. estimate store m7
```

```
. estat icc
```

Residual intraclass correlation

```
------------------------------------------------------------------------------
                Level |       ICC   Std. Err.     [95% Conf. Interval]
----------------------+-------------------------------------------------------
         hospitalnumber |   .2218722   .0543933      .1332766    .3458605
------------------------------------------------------------------------------
```

Model M8

```
. mixed dt bdi visitnodate || hospitalnumber: visitnodate, cov(unst)

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -1305.3017
Iteration 1:   log likelihood = -1303.9384
Iteration 2:   log likelihood =  -1303.935
Iteration 3:   log likelihood =  -1303.935

Computing standard errors:

Mixed-effects ML regression                 Number of obs     =        588
```

```
Group variable: hospitalnumber                Number of groups  =       317

                                              Obs per group:
                                                           min =         1
                                                           avg =       1.9
                                                           max =         3

                                              Wald chi2(2)      =    253.97
Log likelihood =  -1303.935                   Prob > chi2       =    0.0000

------------------------------------------------------------------------------
          dt |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         bdi |    .1651177   .0105221    15.69   0.000     .1444948    .1857406
  visitnodate |   -.1449119   .1240601    -1.17   0.243    -.3880652    .0982413
       _cons |    1.789329   .2562889     6.98   0.000     1.287012    2.291646
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
hospitalnu~r: Unstructured   |
             var(visitn~e) |   .8160859   .3734534      .3328228    2.001053
               var(_cons) |   4.364402    1.51798      2.207339    8.629401
        cov(visitn~e,_cons) |  -1.565429   .7128478     -2.962585    -.168273
-----------------------------+------------------------------------------------
             var(Residual) |   3.245125    .383907      2.573546    4.091955
------------------------------------------------------------------------------
LR test vs. linear model: chi2(3) = 23.21                 Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.

. estimate store m8

. estat icc
```

Conditional intraclass correlation

Level	ICC	Std. Err.	[95% Conf. Interval]	
hospitalnumber	.5735445	.1060801	.3650027	.7588474

Note: ICC is conditional on zero values of random-effects covariates.

. lrtest m8 m7

Likelihood-ratio test LR chi2(2) = 5.26

(Assumption: m7 nested in m8) Prob > chi2 = 0.0722

Note: The reported degrees of freedom assumes the null hypothesis is not on the boundary of the parameter space. If this is not true, then the reported test is conservative.

6.4.7 Time taken to complete, and acceptability questionnaire

Median time taken to complete the DT was 4mins (IQR 3-5mins). 285/324 people (88%) completed the acceptability questionnaire – of these only 4/285 felt upset by being asked to complete the Distress Thermometer, and of the 5/285 who suggested changes, 3 suggested changes to the reference questionnaires and not to the DT itself. One patient objected that the term "Distress Thermometer" was confusing and implied a physical thermometer.

The last complaint did suggest that the patient felt upset by being asked to consider their current quality of life – they felt that their quality of life was poor, and did not want to dwell on this fact. This patient subsequently withdrew from the study. She was offered referral to renal psychology but declined this.

6.5 Discussion

The aims of this study were to assess the construct validity of the Distress Thermometer, to confirm reliability over time, to identify a "cut-off" score for use in clinical practice, and to confirm that the DT itself was quick and easy to use by renal patients, who are often older or disabled. How far have we met these aims?

6.5.1 Is Distress the same thing as Depression?

We found a close relationship between the DT and both the HADS and BDI-II, both in terms of a general correlation between scores, and between higher DT scores and 'caseness' on the HADS and BDI-II, which are unlikely to be due to chance alone.

However there were participants with high levels of distress who did not meet the criteria for 'caseness' on the HADS or BDI-II – for these participants, distress may be due to other issues (pain,

other symptoms, poor quality of life) rather than depression. Equally, some depressed participants had low distress scores. Anhedonia (lack of enjoyment) and withdrawn mood are frequently present in depression but may not be acknowledged as distress by the sufferer.

There was a closer relationship between DT scores and BDI-II scores (AUC 0.87) than between DT scores and HADS scores (AUC 0.76). It is not clear why this should be, however the main difference between the BDI-II and the HADS is that the BDI-II includes questions on somatic symptoms (sleep, appetite) which the HADS excludes (because these may be due to physical illness rather than depression). It is reasonable to suppose that higher DT scores may be related to presence of these somatic symptoms in some patients.

Examining the trajectories of distress it is clear that for some participants, DT scores varied significantly from visit to visit, while the BDI-II and HADS scores did not. It is notable that the ICD-10 diagnostic criteria for depression states that "a duration of at least two weeks is usually required for diagnosis [of depression]" (p120, The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines, World Health Organisation 1992)[319]. This is not the case for distress, which can be transient or prolonged.

The relationship between HADS and DT scores varied over time. Why might this be? We know that HADS scores are fairly stable over time (Figure 6.29) while DT scores vary (Figure 6.28), so perhaps another unidentified factor which influences distress is changing between clinic visits. Whatever this unidentified factor is, it appears to be related to the participant as 64.5% of the variation between DT and HADS scores was due to inter-participant variation.

In contrast, the relationship between BDI-II scores and distress was stable over time, but little of the variation in the relationship (22.2%) was due to differences between participants, which rather begs the question what it is due to in that case.

In terms of choosing a cut-off for 'caseness' for the DT (in order to screen for possible depression), we plotted sensitivity and specificity tables for a range of DT scores (

Table 6.4). The cut off chosen would depend on the aim of the exercise – if you wish to be relatively confident that participants identified really are depressed, ie low false positive rate (eg for a research study) we would recommend a relatively high cut-off of 6 (HADS sensitivity of 41% and specificity of 75%, BDI-II sensitivity of 63% and specificity of 87%) or 7 (HADS sensitivity of 28% and specificity of 90%, BDI-II sensitivity of 47% and specificity of 92%). However, as the low sensitivities demonstrate, this will miss a large number of depressed participants (ie there will be a large false negative rate).

For screening purposes, a lower cut off of 5 (HADS sensitivity of 60% and specificity of 75%, BDI-II sensitivity of 80% and specificity of 75%) would be more useful. There would be false positives, but generally as part of a screening programme there would be a secondary assessment of cases to confirm the diagnosis.

An alternative approach, and indeed the approach that we would support in routine practice, is not to use a cut off at all, but instead to use the DT as an aid to discussion. This should quickly clarify whether DT scores are due to depression or to other factors such as symptoms (ie this would provide the second-level screening).

6.5.2 **How does Distress relate to symptoms and quality of life?**

There was a correlation between increasing MSAS total scores (ie increasing symptom number and/or severity) and distress. It is not possible to establish causation – do the symptoms cause distress, or do distressed patients find their symptoms more burdensome (depressed patients have a reduced pain threshold compared with non-depressed patients[320,321]).

There was an inverse correlation between all subscales of the SF-36, suggesting that distress worsens with worsening quality of life. However, the strongest correlations were between DT score and the Energy and Emotional Wellbeing subscales, rather than (for example) the Physical

Functioning, Physical Role or Pain subscales. This would suggest a mental health component to distress, as opposed to distress being purely a function of physical health limitations.

6.5.3 Acceptability

The response to the Distress Thermometer in the acceptability questionnaire was generally positive. It does appear to be quick to complete, taking most participants approximately 3-5mins.

This is in contrast to the reference questionnaires, which elicited quite a few complaints about the time taken to complete them, the complexity of the questions, and the irrelevance of some of the questions to the participants' situation (for example, the SF-36 asks about "ability to move furniture" and "run for a bus" – there is a clear floor effect here, with very few participants able to do either).

It seems reasonable to conclude that the DT is a quicker and easier tool to complete than the reference questionnaires in this population.

6.5.4 Limitations of the study

The main limitation was the very high dropout rate, disproportionally affecting CKD4/5 patients. The main factor causing this difference in attrition is likely to be the relative ease of taking part for haemodialysis patients, who mostly completed the questionnaires while on dialysis. As they were present on the dialysis unit at predictable times of day it was very easy for the research team to administer the follow up questionnaires, and as many dialysis patients are bored during their dialysis sessions they were quite happy to take part "to pass the time", as one participant put it. In contrast, the CKD4/5 cohort were approached at clinic appointments (which may be rescheduled and may not always run to time) or via post (which is known to have lower response rates)[317].

Efforts were made to approach people for follow up several times, and both stamped-addressed envelopes and telephone reminders were used to try to maximise response rates, but it is likely that any study comparing dialysis patients and community patients will encounter this problem to some extent.

There were also problems with the reference questionnaires chosen: patients reported questionnaire fatigue due to the simultaneous administration of five questionnaires at the same visit; there were floor and ceiling effects in this population as previously discussed (although this is why we wished to find a short easier tool in the first place), and some patients also had difficulty with the complexity of the language used in the reference questionnaires (Americanisms such as "walk around the block", difficulties in categorising frequencies and severities of symptoms in the HADS, BDI-II and MSAS, and difficulty in distinguishing between subtle differences in emphasis in questions in the SF-36). This is not a "test-wise" population[322].

6.5.5 **Unanswered questions**

Although we may conclude that Distress is related to, but distinct from, depression, we need further detail on what exactly the DT measures. Further work examining patient definitions of distress will be useful in clarifying what patients are experiencing when they describe themselves as "distressed" (see Chapter 9).

It is also not clear whether some subgroups (older patients, frailer patients, those with worse renal function) are more distressed than others. Neither do we know what causes distress, and what we as clinicians can do about it.

DT scores were noted to change much more over time than the BDI-II and HADS. It is not clear whether this change over time is due to problems with DT, or whether this is intrinsic to phenomenon of distress.

7 Cross-sectional analysis of distress thermometer scores in haemodialysis and CKD patients

7.1 Introduction

7.1.1 Aims of this study

To assess risk factors affecting DT scores in haemodialysis and CKD4/5 patients

7.1.2 Hypotheses

1. Haemodialysis patients experience significantly higher levels of distress than CKD4/5 patients, even following adjustment for potential confounders such as age, gender and comorbidity.

7.1.3 Outcomes and risk factors of interest

Outcomes: Distress Thermometer score

Risk factors: Treatment modality (CKD4/5 or HD), age, gender, comorbidity score (Charlson and Davies scores), haemoglobin, albumin, eGFR (if CKD4/5), dialysis vintage (if HD), presence of diagnosed depression, peripheral vascular disease, diabetes or heart disease, one-year mortality.

7.1.4 Study design

This was a prospective cohort study.

7.2 Methods

7.2.1 Study setting and data collection

This study used the same dataset as the validation study (ethic committee approval was obtained for this further use, see Appendix A). See Chapter 6 for details of study setting, recruitment and data collection.

We did not have access to data regarding co-morbidities or mortality for the Lister participants, so limited our analysis to the Royal Free patients, giving a sample size of 287 (139 haemodialysis patients, 138 CKD patients).

7.2.2 Power calculation for cross-sectional study

As the dataset collected for the validation study was also used in the cross-sectional study (Chapter 4), a power calculation was performed in Stata to ensure that we had sufficient data available to detect a difference between the low clearance and haemodialysis cohorts. Although a pre-study sample size calculation would have been preferable, no prior data existed regarding the DT score in haemodialysis and low clearance patients and so a post-hoc analysis had to be performed.

Assuming an alpha of 0.05, and using the means and standard deviations obtained in chapter 4 (CKD4/5 patients: mean =2.46, st dev= 2.50. haemodialysis patients: mean= 4.13, st dev=2.82), the study had a power of 0.9997. Indeed, our study was adequately powered to detect any difference in mean DT scores ≥ 1 unit.

7.2.3 Statistical analysis

We first described the sample, and the prevalence/distribution of each of the risk factors of interest. We calculated whether there was a difference in mean values between the CKD4/5 cohort and the

RRT cohort for each risk factor using the unpaired t-test, giving 95% confidence intervals and p-values.

We assessed the normalcy of the distribution of the DT, and of each of the other risk factors of interest. The DT scores did not follow a normal distribution, so the Wilcoxon Rank-Sum test was used to determine whether there was a significant difference between the CKD4/5 patients and the haemodialysis patients.

We plotted scatter graphs of DT scores and the continuous risk factors of interest, and used Spearman's Rank Correlation to assess the strength of the association between them, and whether this relationship was statistically significant. We plotted histograms of DT scores stratified by each of the possible outcomes for the categorical risk factors of interest, showing the median DT score for each category. We used the Wilcoxon Rank-Sum test to test the hypothesis that there was no relationship between DT scores and each outcome of the risk factor in question.

We constructed a model of factors affecting DT scores, fitting models of progressive complexity and using Likelihood-ratio tests to assess whether each extra risk factor improved the fit of the model. We assessed models which included each of the risk factors which we had found to be significantly associated with DT scores in the previous section, discarding those risk factors which did not improve the fit of the model, in order to keep the model as simple as possible without sacrificing accuracy.

7.2.4 **Missing data**

When questionnaire responses were missing, this was dealt with using pairwise deletion - the outcome measure which had data missing was excluded from the statistical analysis, but any other completed tools provided by that patient were included in the analysis.

7.3 Results

7.3.1 Size of cohort and participant characteristics

We did not have access to data regarding co-morbidities or mortality for the Lister participants, so limited our analysis to the Royal Free patients, giving a sample size of 273 (134 CKD4/5 patients, 139 haemodialysis patients).

The mean age was 63.2 years in the CKD4/5 cohort, and 65.7 years in the HD cohort. 64% of the CKD4/5 and 72% of the HD cohort were male. This is in keeping with our centres' renal populations, and reflects that of the UK as a whole *(UKRR 17th Annual Report[315]).* The median eGFR in the CKD 4/5 cohort was 18mls/min (MDRD equation), and the median dialysis vintage for the HD cohort was 27 months.

The prevalence of previously-diagnosed depression was very similar in both cohorts (12.2% in the CKD4/5 cohort and 14.6% in the HD cohort). The HD cohort had a slightly higher prevalence of ischaemic heart disease, peripheral vascular disease and diabetes, although these differences did not reach statistical significance. Despite this, comorbidity scores (both Charlson and Davies comorbidity scores) were the same across both cohorts.

Haemoglobin was higher in the CKD 4/5 cohort (115g/L vs 105g/L in the HD cohort, $p<0.001$), as was serum albumin (41.5g/L in CKD4/5 cohort and 39.2g/L in HD cohort, $p<0.001$). This may be due to higher levels of infection and inflammation in haemodialysis patients. Other characteristics of the study population are summarised in Table 4.1.

Table 7.1 Characteristics of study population, by modality

	CKD 4/5 (Mean, 95% CI)	Haemodialysis (Mean, 95% CI)	Unpaired t-test p values
Age	63.2 (60.2 – 66.2)	65.7 (63.2 – 68.2)	0.212
Male Gender	63.6% (55.3 – 72.0)	72.3% (64.7 – 79.9)	0.130
Davies score	1.5 (1.3 – 1.8)	1.7 (1.5 – 2.0)	0.301
Charlson comorbidity index	6.1 (5.6 – 6.6)	6.3 (5.9 – 6.7)	0.506
Haemoglobin (g/L)	115 (112 – 118)	109 (107 – 111)	<0.001
Serum Albumin(g/L)	41.5 (40.8 – 42.2)	39.2 (38.5 – 40.8)	<0.001
eGFR (mls/min)	18	n/a	
Months on HD	n/a	27	
Diagnosis of depression	12.1% (6.5 – 17.8)	14.6% (8.6 – 20.6)	0.552
PVD	14.4% (8.3 – 20.5)	24.1% (16.8 – 31.3)	0.044
IHD	34.8% (26.6 – 43.1)	40.9% (32.5 – 49.2)	0.310
Diabetes	37.9% (29.5 – 46.3)	46.0% (37.5 – 54.4)	0.179
One-year mortality	7.5% (3.0 – 12.0)	5.0% (1.4 – 8.7)	0.409

7.3.2 **Assessment of normality for continuous variables**

We saw in Chapter 3 that DT scores are non-normally distributed.

Age at assessment showed a left-skewed distribution, with a mean age of 64.5 years and a median of 67.4 years (IQR 52.0 – 77.2) (Figure 7.1).

Haemoglobin (Figure 7.2 and serum albumin results (Figure 7.3) appear to be normally distributed.

EGFR (Figure 7.4) does appear to be normally distributed, with censoring at both tails – this is due to the referral criteria for Low Clearance clinic where these patients were recruited (patients must have an eGFR below 20mls/min, or 30mls/min if diabetic, to be referred. Patients with very low eGFRs (<5mls/min) are likely to have either started dialysis or to be too ill to attend).

Dialysis vintage (Figure 7.5) appears to follow a gamma distribution – this is unsurprising as this graph essentially represents survival time on dialysis.

Charlson Comorbidity Index (Figure 7.6) and Davies comorbidity scores (Figure 7.7) appear to be fairly normally distributed, despite a "floor" effect (probably due to the age of our cohort) censoring the lower end of the CCI distribution, and a little left-skewing of the Davies distribution.

Figure 7.1 Age distribution across whole cohort (years)

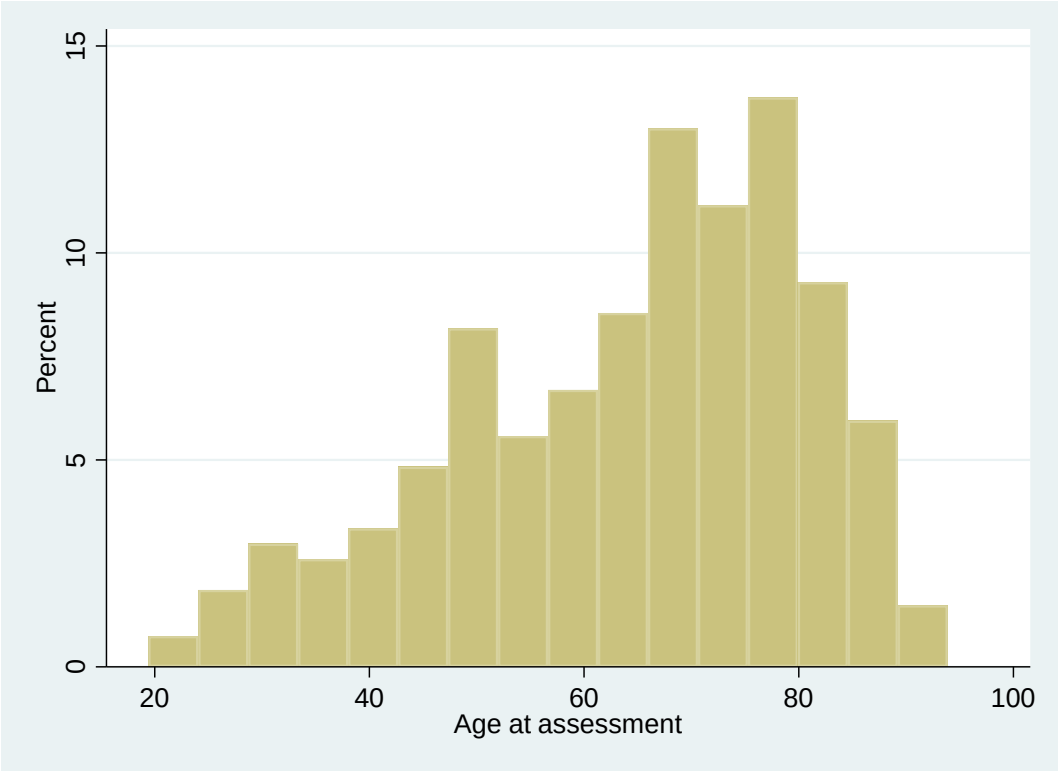


Figure 7.2 Distribution of Haemoglobin results

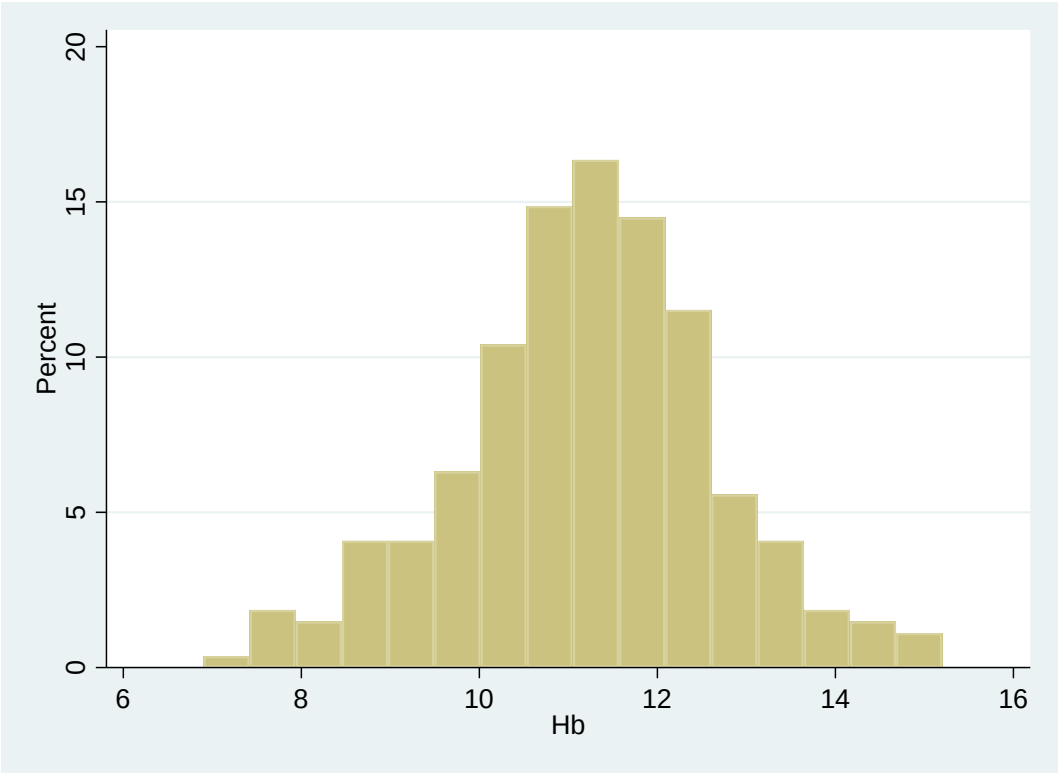


Figure 7.3 Distribution of Serum Albumin results

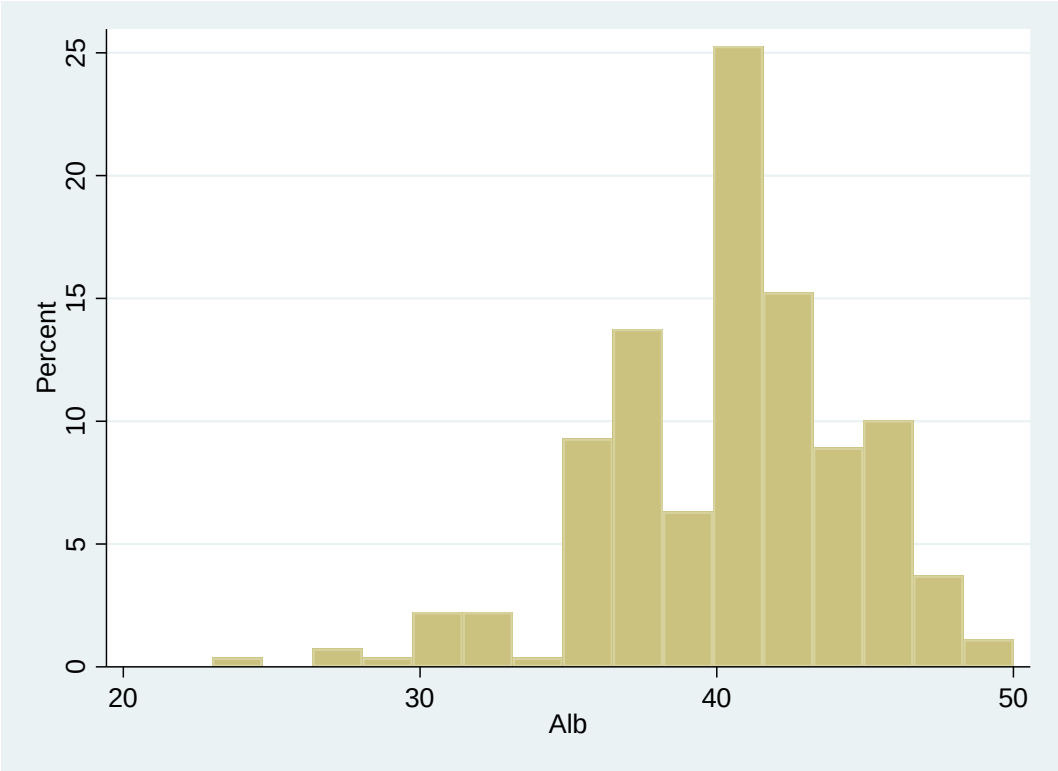


Figure 7.4 Distribution of eGFR results (CKD 4/5 patients only)

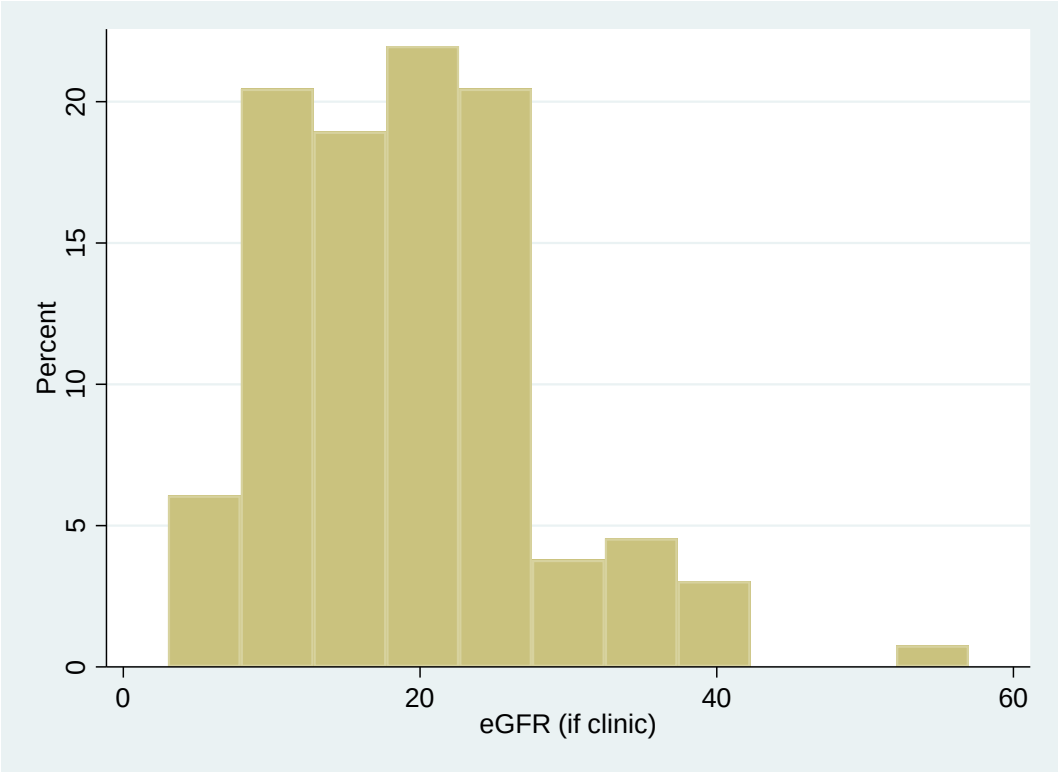


Figure 7.5 Dialysis vintage (months) (HD patients only)

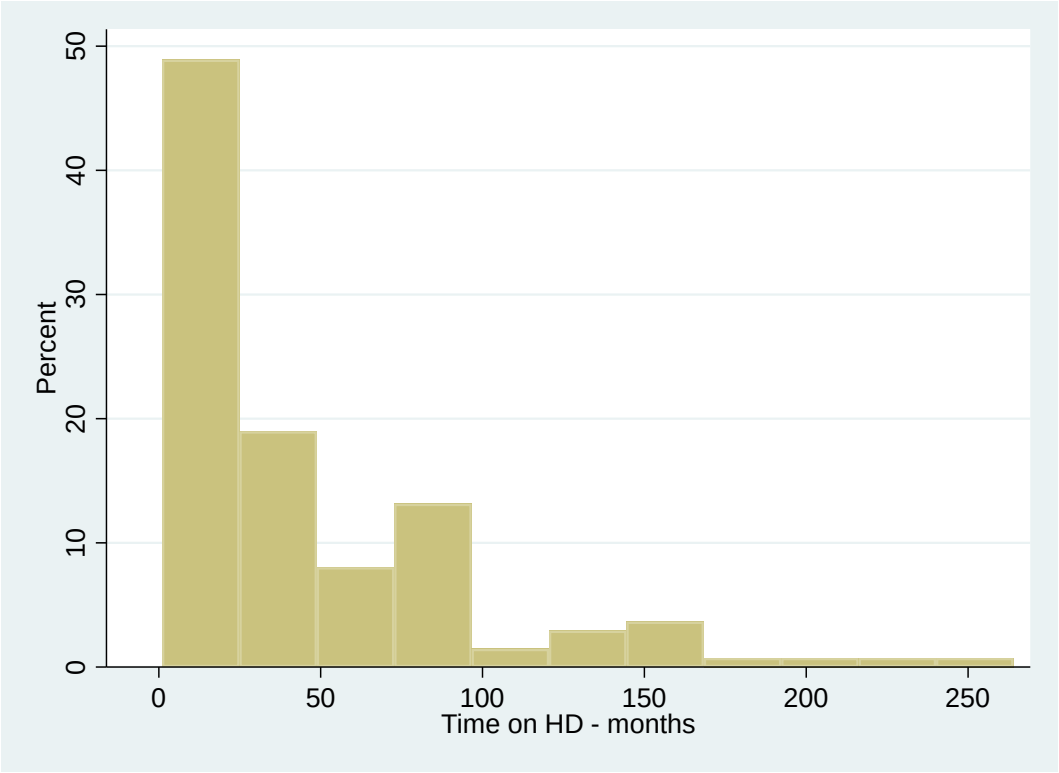


Figure 7.6 Distribution of Charlson Comorbidity Index scores

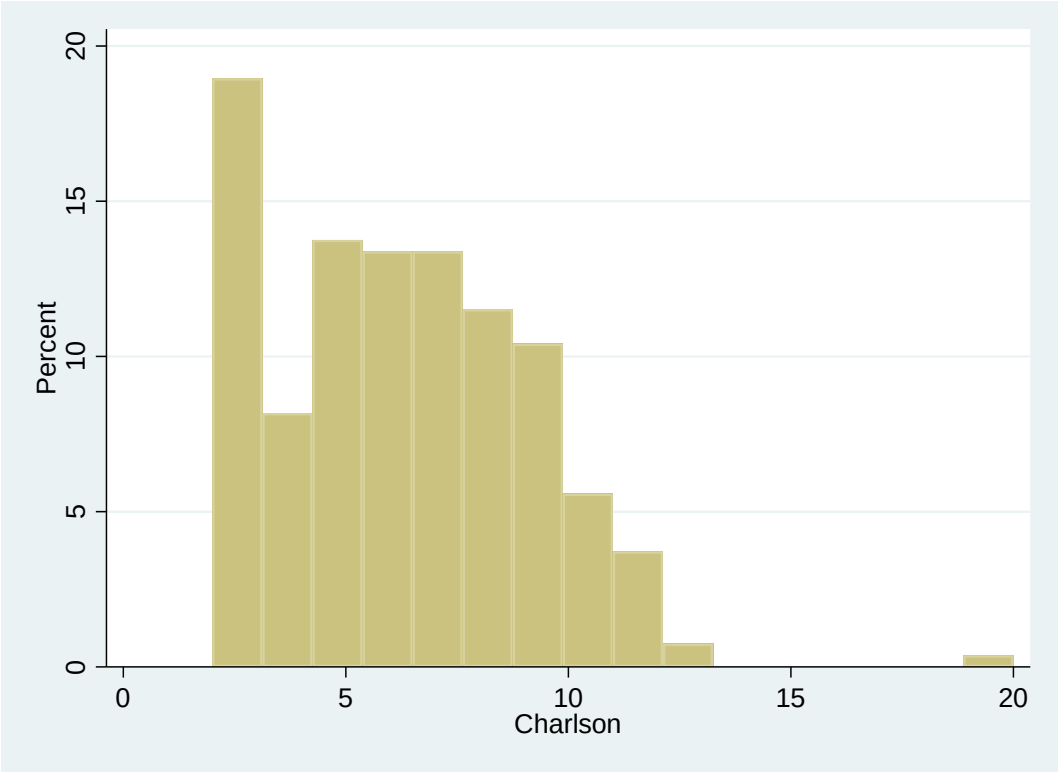
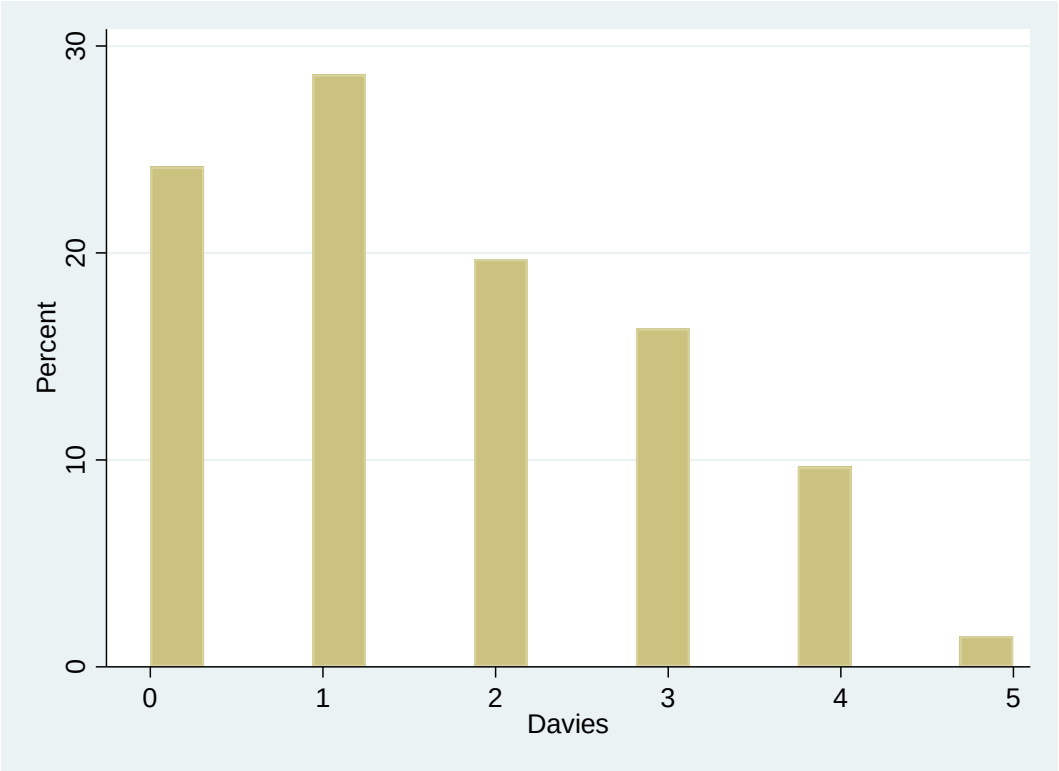


Figure 7.7 Distribution of Davies comorbidity scores



7.3.3 Differences in distribution of DT scores in CKD4/5 patients and HD patients

Figure 7.8 and
Figure 7.9 show the distribution in DT scores in CKD 4/5 patients and HD patients respectively. DT scores appear to be much more normally distributed in the HD patients following this stratification (which suggests that the non-normality may be due to the cohort containing several overlapping subpopulations rather than anything intrinsic to the DT itself). DT scores are still non-normally distributed in CKD4/5 patients, with a significant floor effect at "0". Median DT score was 2 for CKD4/5 patients (IQR 0 – 5) and 4 for HD patients (IQR 2 – 6).

As the DT scores are non-normally distributed, the two-sample Wilcoxon rank-sum test was used to test the hypothesis that there was no difference between CKD4/5 and HD patients' DT scores. P < 0.001, suggesting this is a significant difference in DT scores between the two groups.

```
. ranksum dt, by( rrtclinic )

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

  rrtclinic |     obs    rank sum    expected
------------+---------------------------------
     Clinic |     131      14651     17619.5
        RRT |     137      21395     18426.5
------------+---------------------------------
   combined |     268      36046      36046

unadjusted variance   402311.92
adjustment for ties    -7656.62
                    ----------
adjusted variance     394655.30

Ho: dt(rrtcli~c==Clinic) = dt(rrtcli~c==RRT)
           z =  -4.725
    Prob > |z| =   0.0000
```

Figure 7.8 Distress Thermometer scores (CKD 4/5 patients). Median = 2

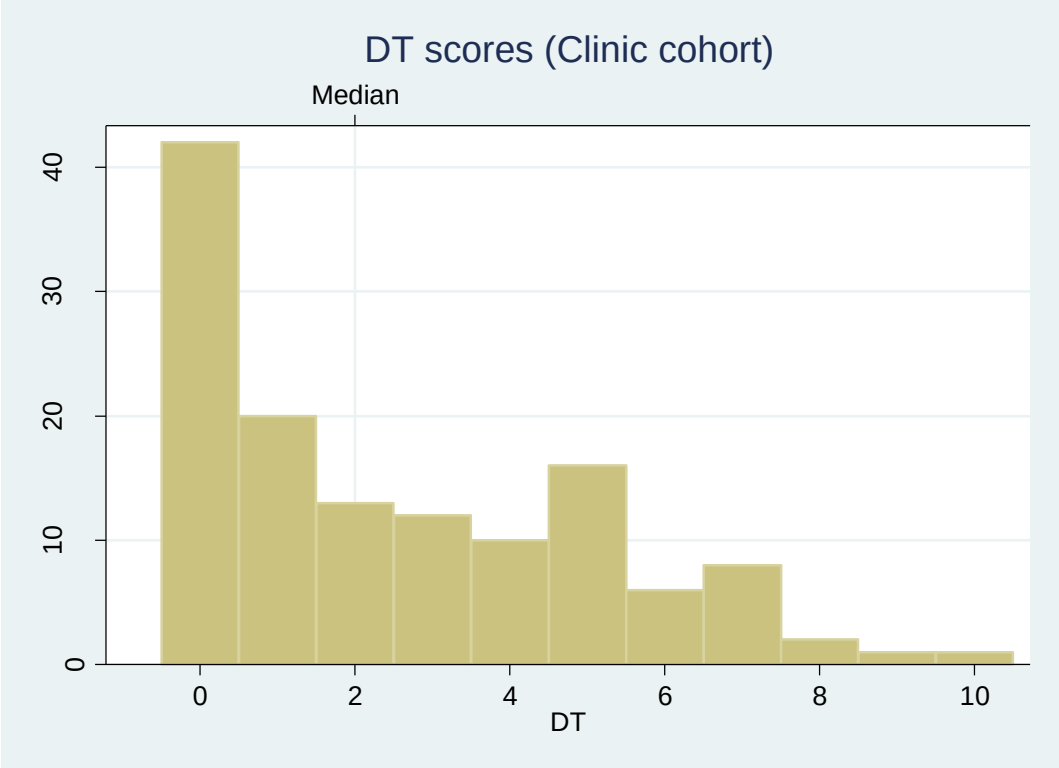
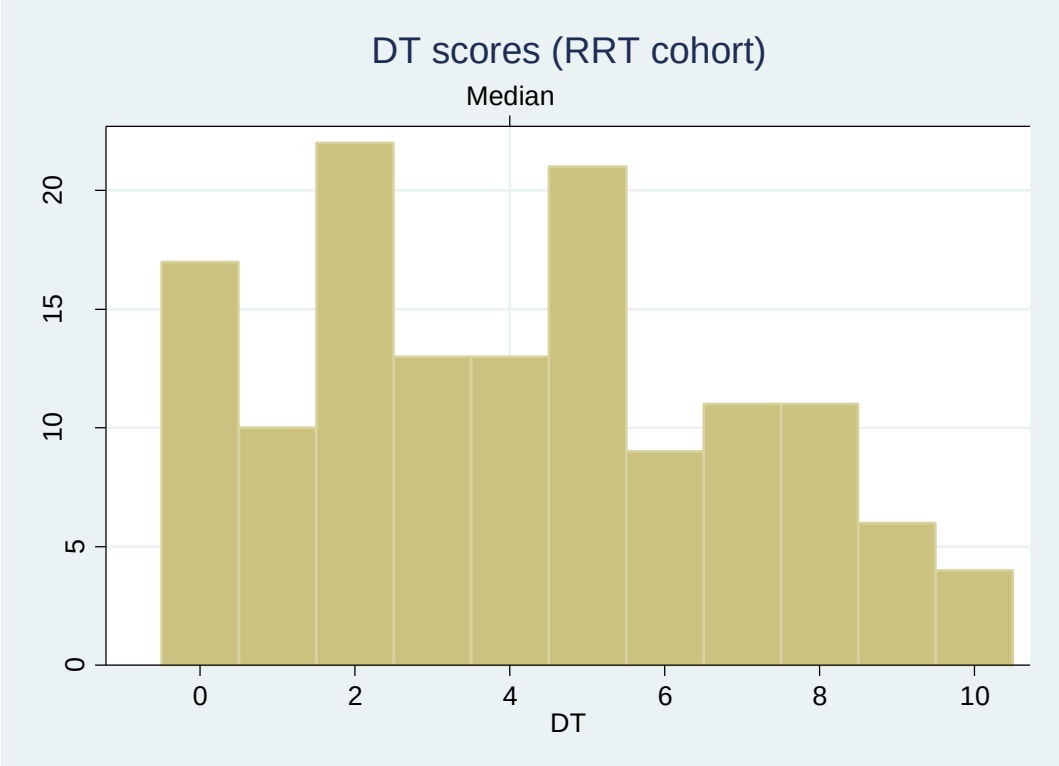


Figure 7.9 Distress Thermometer scores (HD patients) Median = 4

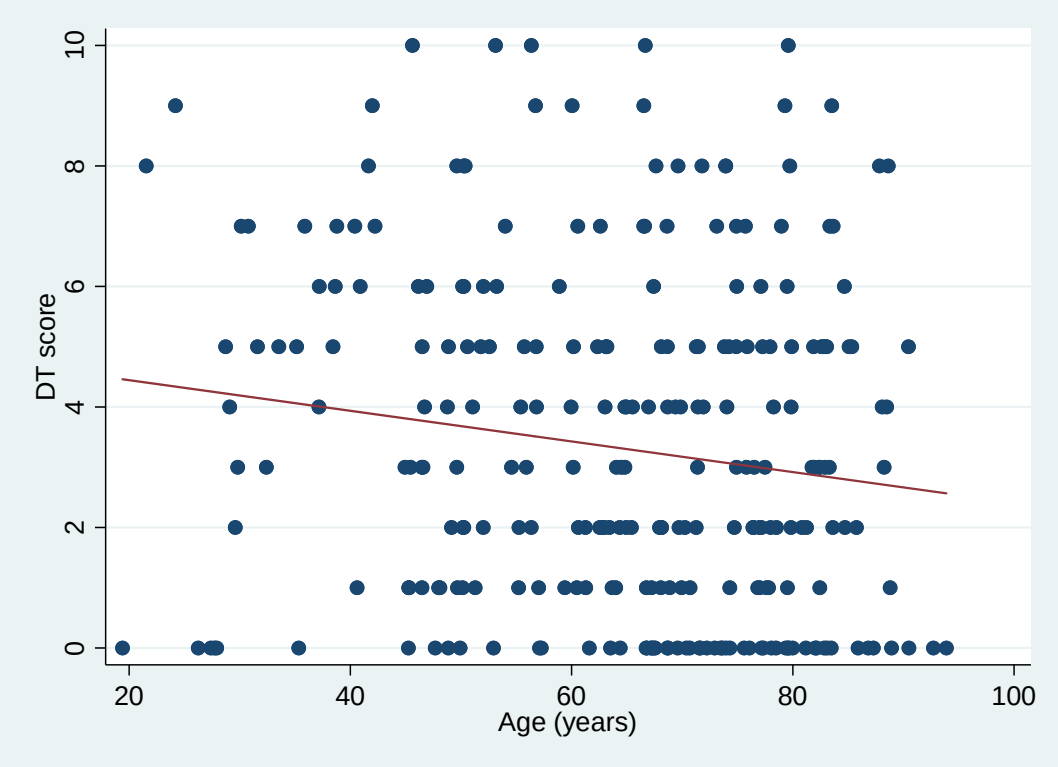


7.3.4 Association between DT scores and continuous variables

As the DT scores were non-normally distributed, we used Spearman Rank Correlation to assess the relationship between DT scores and the continuous risk factors of interest.

DT score and age

Figure 7.10 Relationship between DT score and increasing age



We see from the scatter graph above (Figure 7.10) that DT scores appear to be *lower* in older patients. This is unexpected, as it had been hypothesised that older patients would have poorer health and worse quality of life, and thus would be more likely to be distressed.

. spearman dt ageatassessment, stats(p)

Number of obs = 264
Spearman's rho = -0.1463

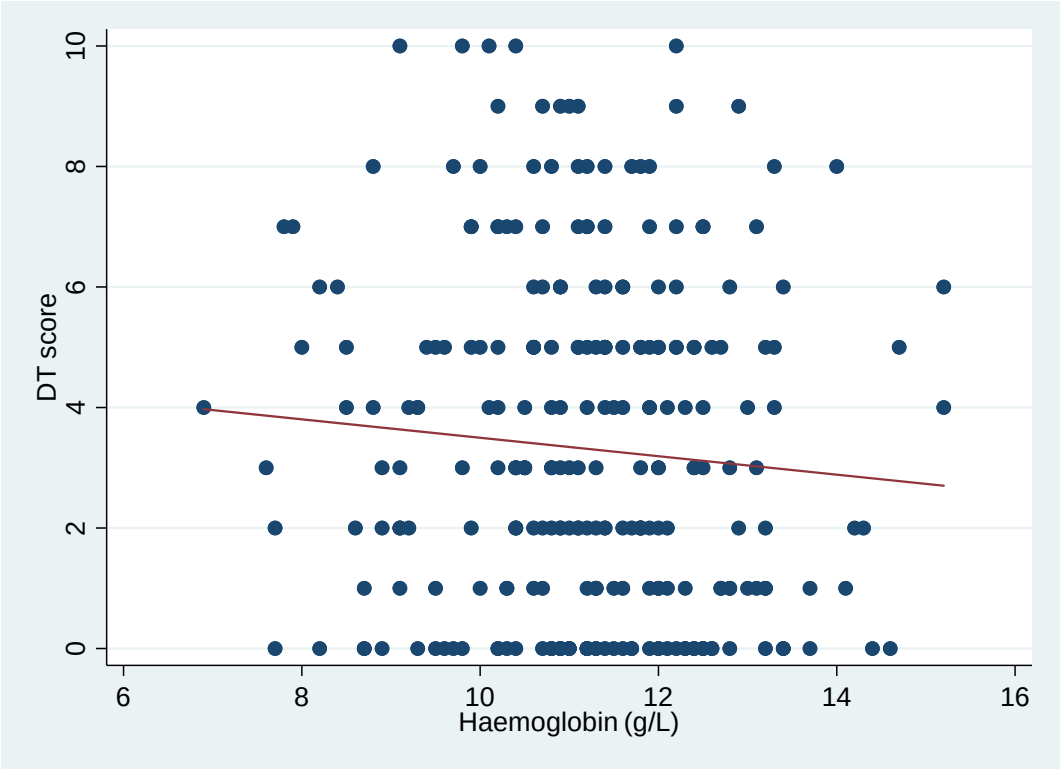
Test of Ho: dt and ageatassessment are independent

Prob > t = 0.0174

Spearman's rho was -0.1463, and p = 0.0174, which suggests that there is a relationship between age and DT.

DT score and Haemoglobin

Figure 7.11 Relationship between DT score and haemoglobin



The correlation between DT score and haemoglobin appears to be extremely weak. It appears that there is a slight reduction in distress as haemoglobin increases, however this is not a statistically significant relationship.

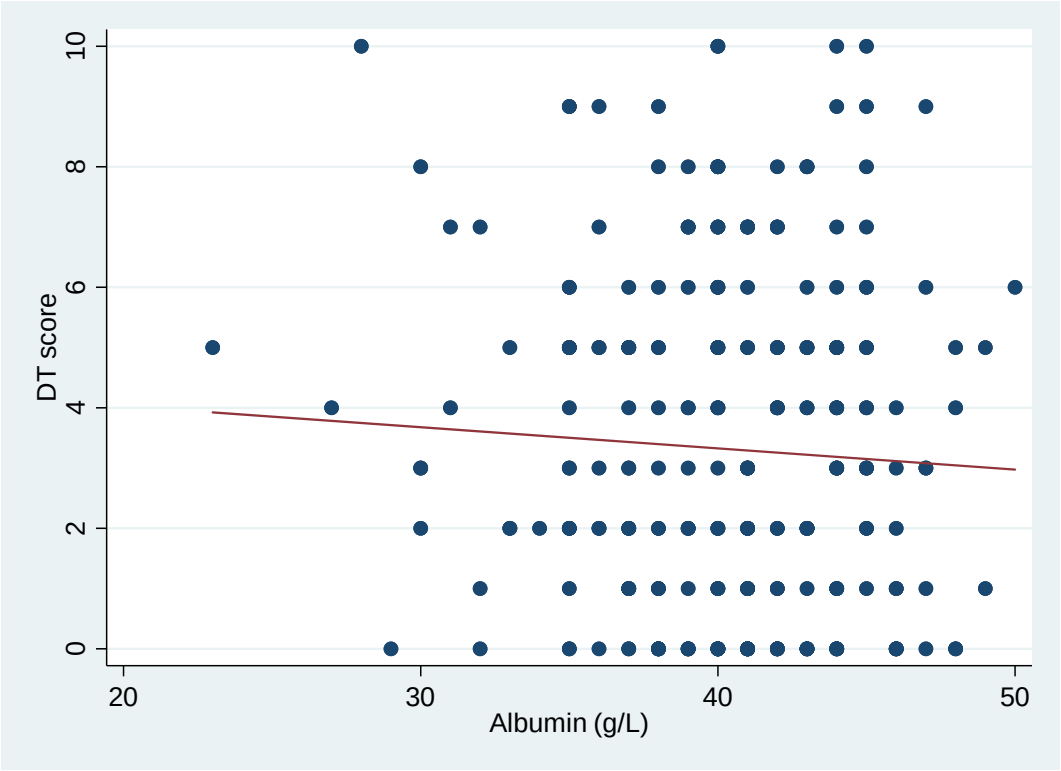
. spearman dt hb, stats(p)

Number of obs = 264
Spearman's rho = -0.0892

Test of Ho: dt and hb are independent
Prob > |t| = 0.1484

DT score and Serum Albumin

Figure 7.12 Relationship between DT score and Serum Albumin



There does not appear to be any correlation between DT score and serum albumin. Spearman's rho is -0.0371, and p = 0.5480.

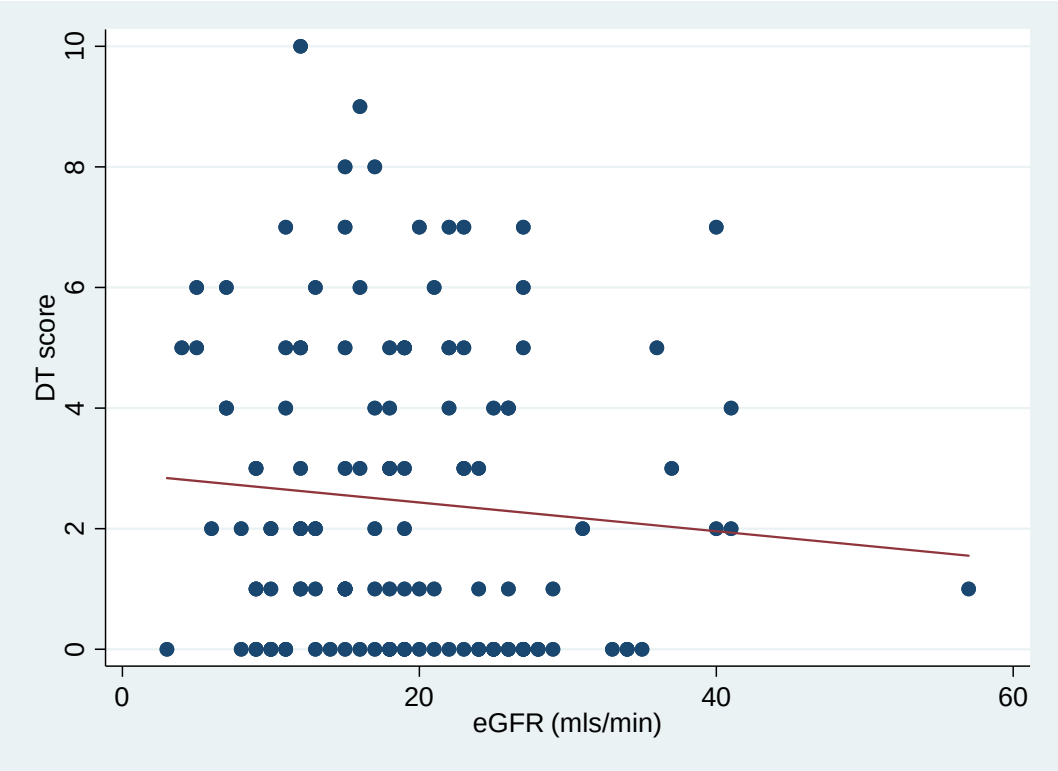
. spearman dt alb, stats(p)

Number of obs = 264
Spearman's rho = -0.0371

Test of Ho: dt and alb are independent
Prob > |t| = 0.5480

DT score and eGFR (CKD4/5 patients only)

Figure 7.13 Relationship between DT score and eGFR



There does appear to be a very slight negative correlation between DT score and eGFR in our CKD4/5 cohort – ie as renal function worsens, distress increases. However, Figure 7.13 shows that the distribution of results is very wide with many outliers, and the relationship between DT score and eGFR does not reach statistical significance.

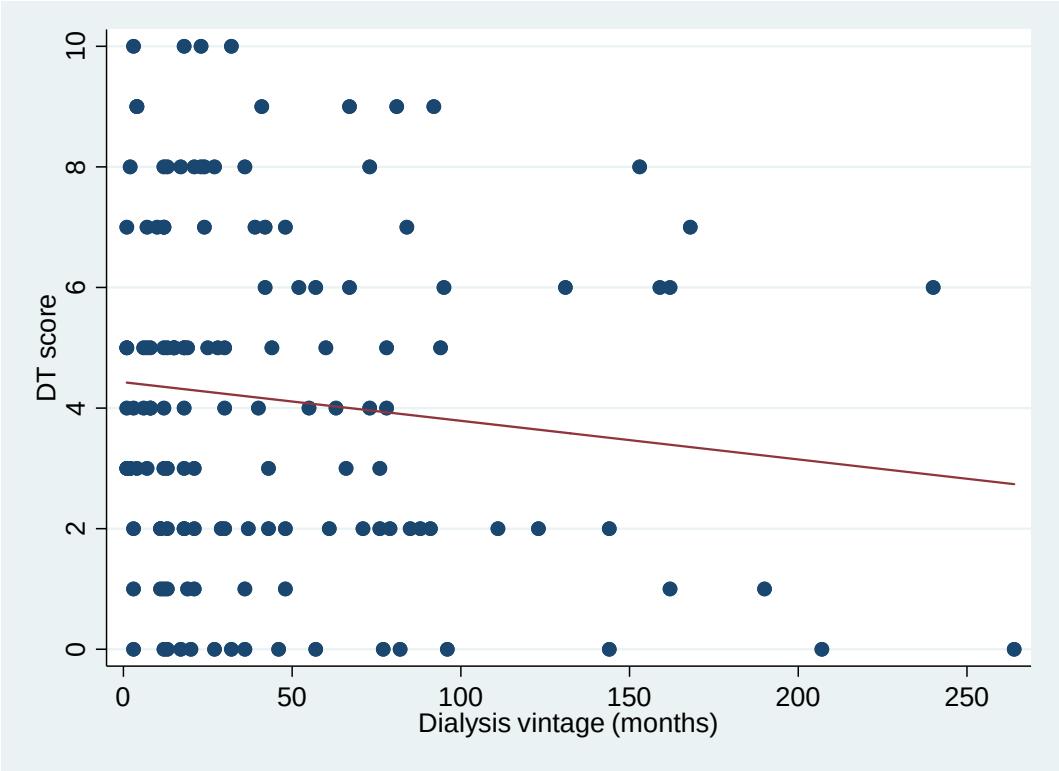
. spearman dt egfrifclinic if modality==0, stats(p)

Number of obs = 129
Spearman's rho = -0.1138

Test of Ho: dt and egfrifclinic are independent
Prob > |t| = 0.1991

DT score and dialysis vintage (months) (HD patients only)

Figure 7.14 Relationship between DT score and dialysis vintage (months)



There appears to be a very slight negative correlation between time since initiation of dialysis in months, and DT scores (ie distress improves as dialysis vintage increases). It is not clear what the causal relationship might be here: does distress abate as patients adjust to their new life on dialysis? Or do the highly-distress patients have lower survival on dialysis?

The relationship appears to be extremely weak, and does not reach statistical significance (p = 0.2845).

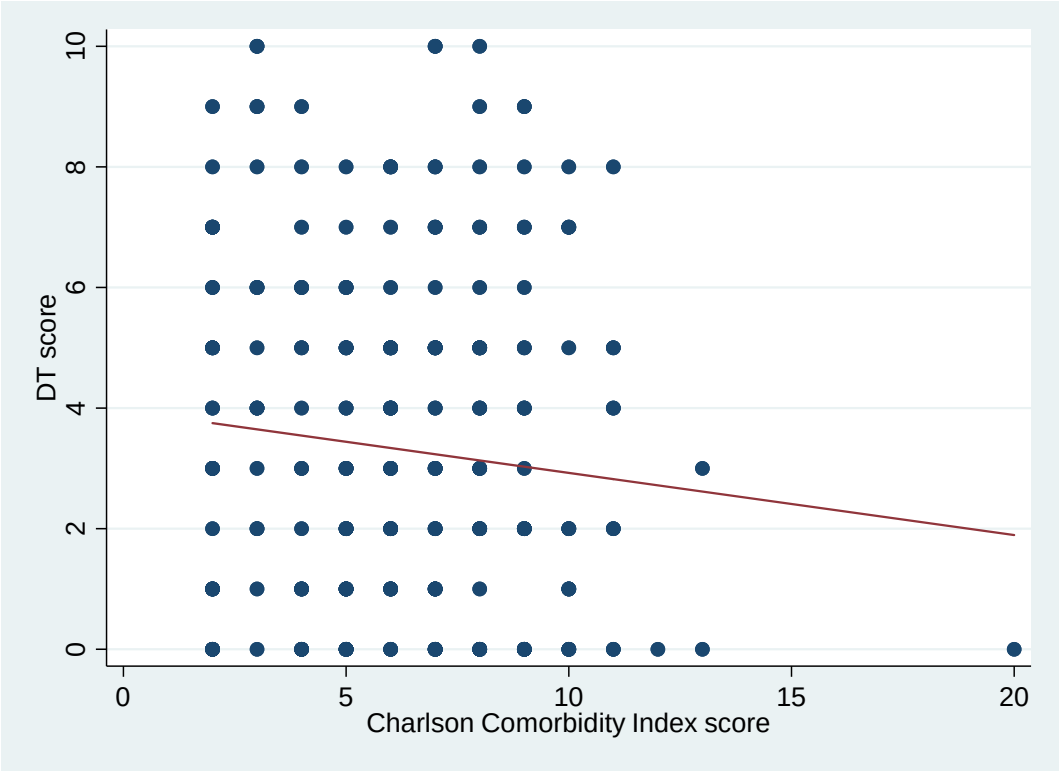
. spearman dt timeonhdmonths if modality==1, stats(p)

Number of obs = 135
Spearman's rho = -0.0928

Test of Ho: dt and timeonhdmonths are independent
Prob > |t| = 0.2845

DT score and Charlson Comorbidity Index score

Figure 7.15 Relationship between DT score and CCI score



It is interesting to see that the relationship between DT score and Charlson Comorbidity Index appears to be negative – as CCI increases, DT score reduces. One might expect the reverse. However CCI contains an age component, and Figure 7.10 showed a negative relationship between DT score and age – it may be that we are simply seeing the effect of age again.

The relationship appears to be very weak, and not statistically significant.

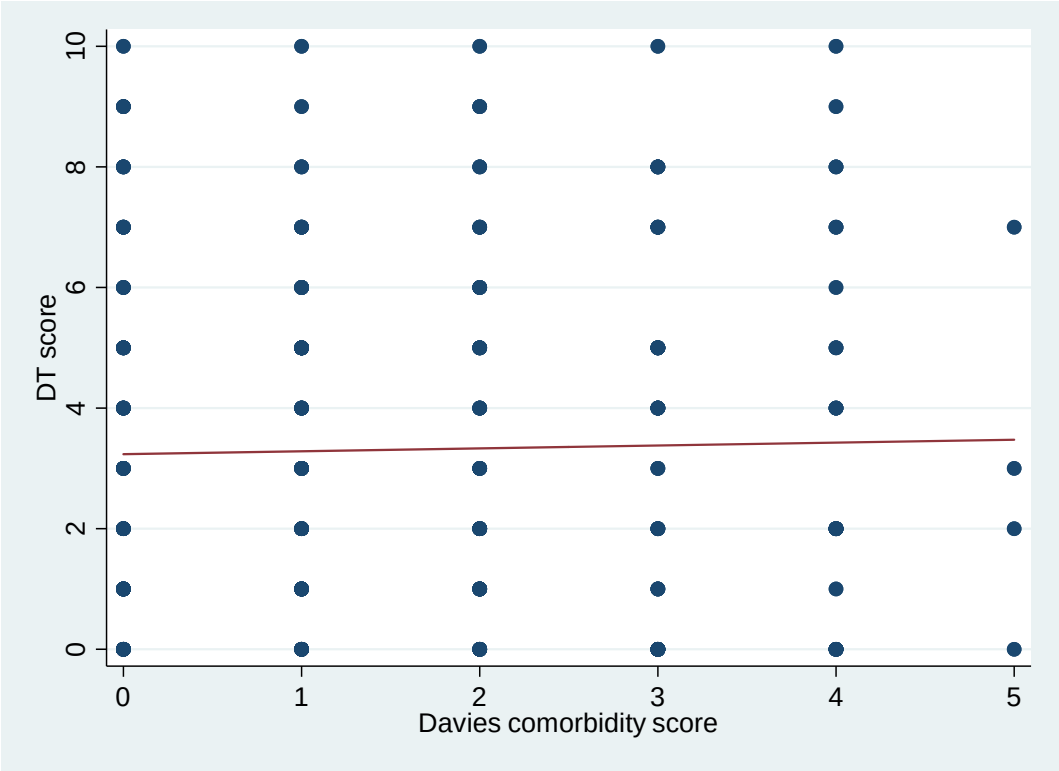
. spearman dt charlson , stats(p)

Number of obs = 264
Spearman's rho = -0.0851

Test of Ho: dt and charlson are independent
Prob > |t| = 0.1678

DT score and Davies comorbidity score

Figure 7.16 Association between DT score and Davies comorbidity score



In contrast to the CCI, the Davies comorbidity score does not contain an age component, and it is interesting to see that the relationship between DT and Davies score is positive (ie increasing comorbidity is associated with increasing distress).

Again this effect is very weak, and not statistically significant in this sample.

. spearman dt davies , stats(p)

Number of obs = 264
Spearman's rho = 0.0153

Test of Ho: dt and davies are independent
Prob > |t| = 0.8050

7.3.5 Association between DT scores and categorical variables

Gender

Figure 7.17 Difference in DT scores between Male and Female patients

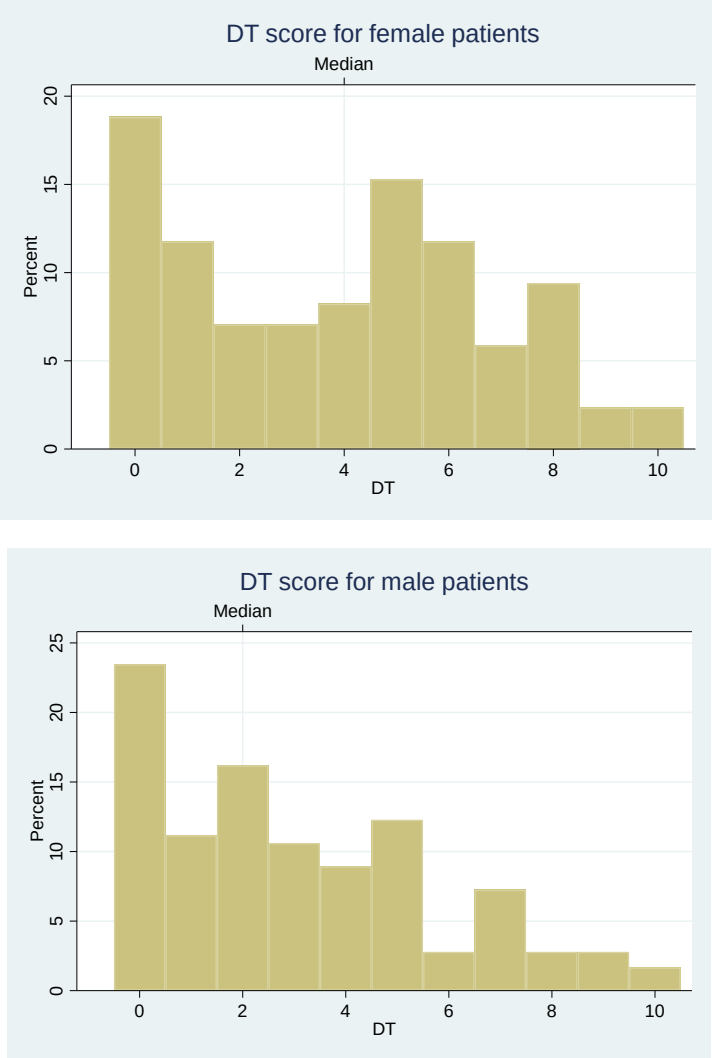


Figure 7.17 shows the distribution in DT scores for male and female patients. Median score for male patients is 2, and for female patients is 4. This is somewhat significant (p = 0.027)

. ranksum dt, by(gender)

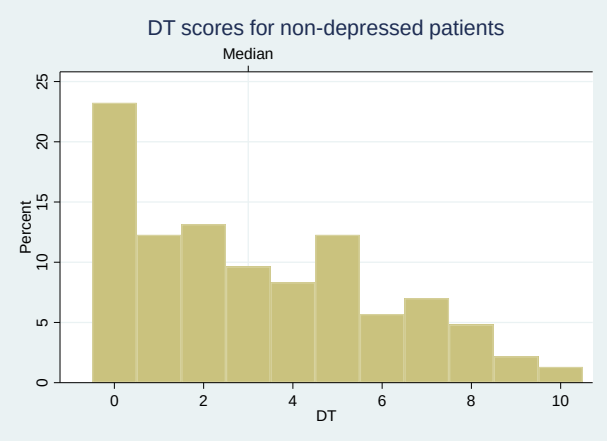
Two-sample Wilcoxon rank-sum (Mann-Whitney) test

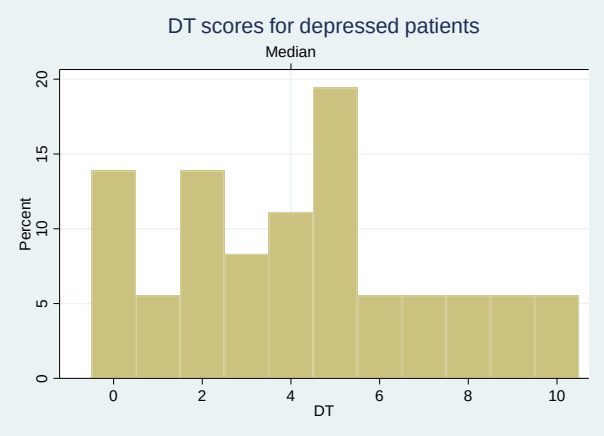
gender	obs	rank sum	expected
0	85	12532.5	11262.5
1	179	22447.5	23717.5

```
-------------+---------------------------------
    combined |      264       34980       34980

unadjusted variance   335997.92
adjustment for ties    -6341.45
                    ----------
adjusted variance     329656.47

Ho: dt(gender==0) = dt(gender==1)
           z =   2.212
    Prob > |z| =   0.0270
```

Depression

Figure 7.18 Differences in DT score between depressed and non-depressed patients





There were surprisingly few patients (36/264) with a formal diagnosis of depression, given the number of "cases" on the HADS and BDI-II. This may account for the very small difference between distress in patients who had a formal diagnosis of depression, and those who did not. Median score for depressed patients is 4, and for non-depressed patients is 3. P = 0.046.

. ranksum dt, by(depression)

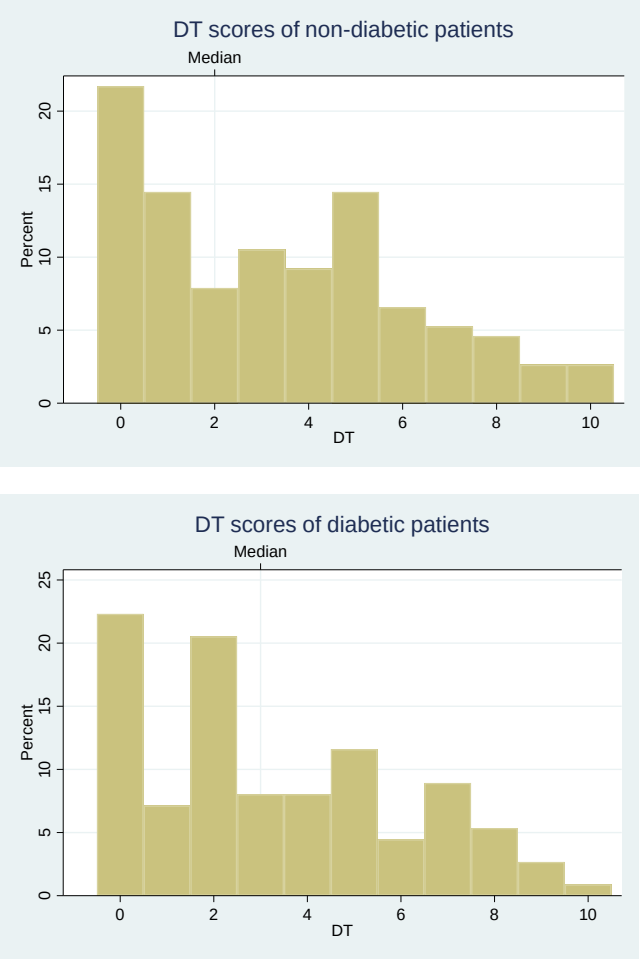
Two-sample Wilcoxon rank-sum (Mann-Whitney) test

depression	obs	rank sum	expected
0	228	29367.5	30210

```
        1 |      36     5612.5       4770
-------------+--------------------------------
    combined |     264      34980      34980

unadjusted variance   181260.00
adjustment for ties    -3421.00
                    ----------
adjusted variance     177839.00

Ho: dt(depres~n==0) = dt(depres~n==1)
           z =  -1.998
    Prob > |z| =   0.0457
```

DT score and Diabetes

Figure 7.19 Differences in DT scores between diabetic and non-diabetic patients



There was no apparent difference in DT scores between diabetic and non-diabetic patients. Although the median DT score for diabetic patients was 3 and for non-diabetic was 2, p = 0.902.

. ranksum dt, by (diabetesyn)

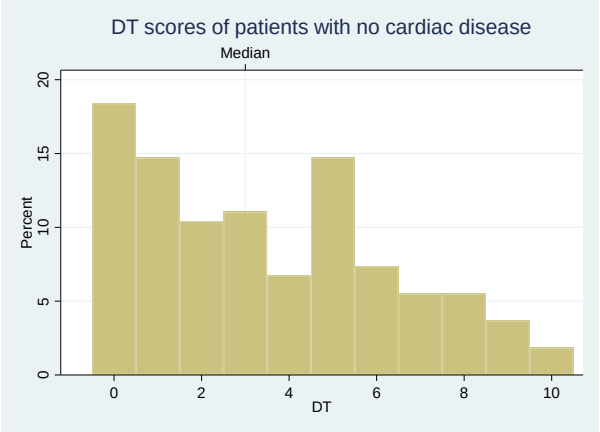
Two-sample Wilcoxon rank-sum (Mann-Whitney) test

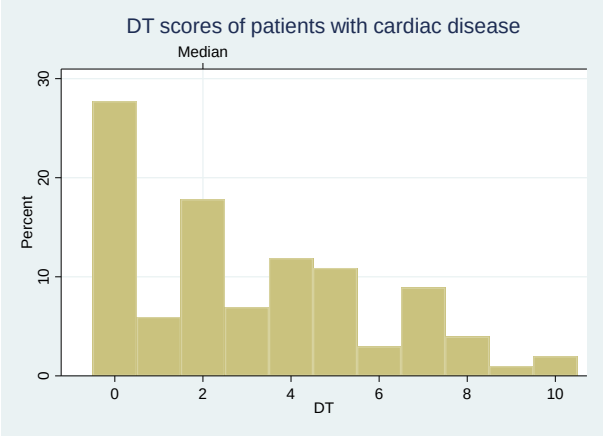
diabetesyn	obs	rank sum	expected
0	152	20214.5	20140
1	112	14765.5	14840

```
    combined |      264       34980       34980

unadjusted variance   375946.67
adjustment for ties    -7095.42
                    ----------
adjusted variance     368851.25

Ho: dt(diabet~n==0) = dt(diabet~n==1)
           z =   0.123
    Prob > |z| =   0.9024
```

DT score and cardiac disease

Figure 7.20 Differences in DT scores between patients with and without a diagnosis of cardiac disease





There was no apparent difference in distress scores between patients with a diagnosis of cardiac disease (median = 2) and patients with no cardiac disease (median = 3) (p = 0.194).

. ranksum dt, by (heartdiseaseyn)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

heartdisea~n	obs	rank sum	expected
0	163	22373.5	21597.5
1	101	12606.5	13382.5
combined	264	34980	34980

unadjusted variance 363557.92

adjustment for ties -6861.60

---

adjusted variance 356696.32

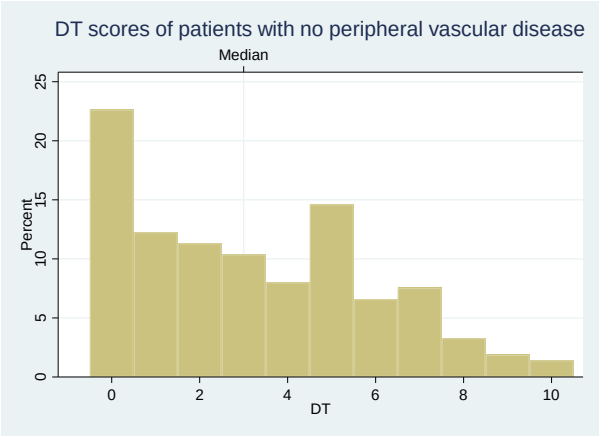
Ho: dt(heartd~n==0) = dt(heartd~n==1)

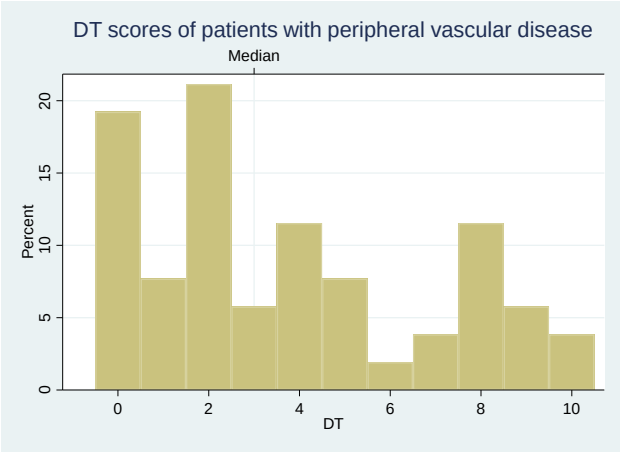
z = 1.299

Prob > |z| = 0.1938

Peripheral Vascular Disease

Figure 7.21 Difference in DT scores between patients with and without PVD





There was no apparent difference in distress scores between patients with a diagnosis of peripheral vascular disease (median = 3) and patients with no peripheral vascular disease (median = 3) (p = 0.377).

. ranksum dt, by (pvd)

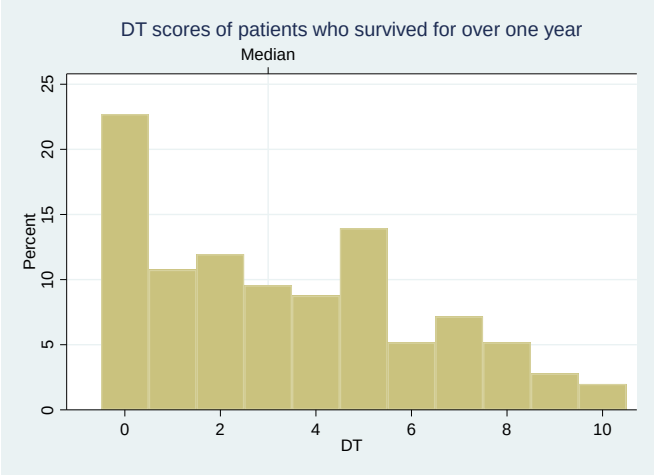
Two-sample Wilcoxon rank-sum (Mann-Whitney) test

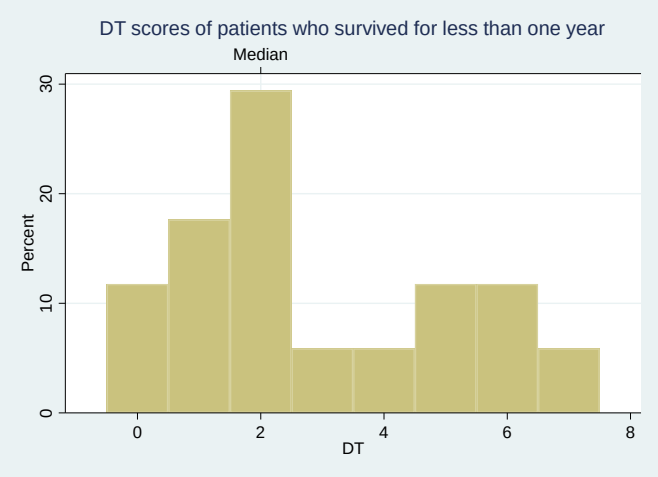
pvd	obs	rank sum	expected
0	212	27658	28090

```
        1 |      52       7322       6890
----------+--------------------------------
   combined |     264      34980      34980

unadjusted variance   243446.67
adjustment for ties    -4594.68
                    ----------
adjusted variance     238851.98

Ho: dt(pvd==0) = dt(pvd==1)
           z =  -0.884
   Prob > |z| =   0.3767
```

One-year mortality

Figure 7.22 Difference in DT scores between patient who survived for > 1 year, and those who did not





There was no difference in DT scores in those patients who died with a year of taking part in the study, as compared with those patients who survived for more than one year. Median DT score in both groups was 2, and two-sample Wilcoxon rank-sum test gave p = 0.695.

. ranksum dt, by (mortality)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

mortality	obs	rank sum	expected

```
        0 |     251    33879.5    33759.5
        1 |      17     2166.5     2286.5
----------+--------------------------------
   combined |     268      36046      36046

unadjusted variance    95651.92
adjustment for ties    -1820.40
                    ----------
adjusted variance      93831.51

Ho: dt(mortal~y==0) = dt(mortal~y==1)
           z =   0.392
    Prob > |z| =   0.6952
```

7.3.6 Model of factors affecting DT scores

We attempted to model which of the risk factors examined in the previous section affect DT score, using multiple regression analysis.

We first tried to transform the DT scores to produce a normal distribution, in order to make regression analysis easier. We tried squaring, inverting, and both logarithmic and natural log transformations, but none of these transformations improved the normalcy of the sample. This is likely due to the high frequency of "0" scores (which will not change during these transformations – for example $0^2 = 0$, $1/0 = 0$, etc).

We therefore decided to continue using the untransformed values in the model, as it was felt that the non-normal distribution was due primarily to multiple overlapping subgroups within the sample. It was hoped that by stratifying by the various risk factors of interest, we might tease out the different normally-distributed subgroups.

We transformed “age” by squaring it, as this gave a more normal distribution:

Figure 7.23 Age (before square transformation)

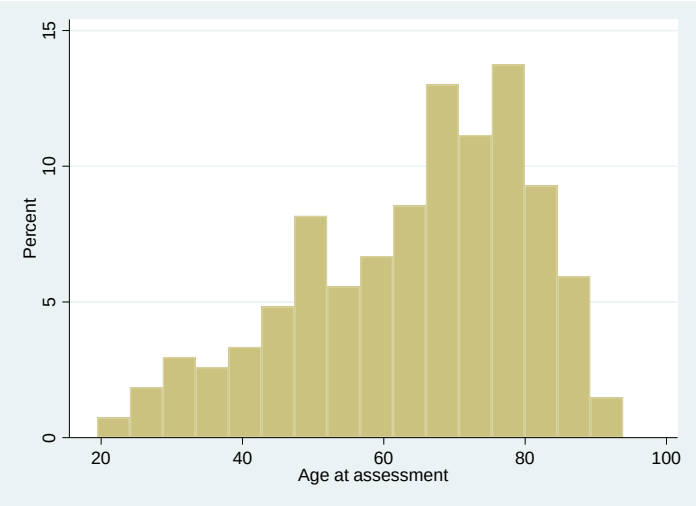
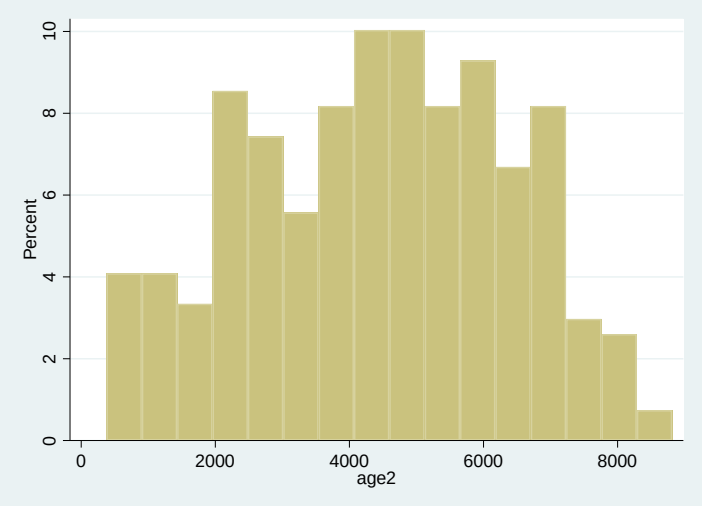


Figure 7.24 Age^2 (after square transformation)



The other risk factors from sections 7.3.3, 7.3.4 and 7.3.5 which reached statistical significance were dialysis modality, age, gender and diagnosis of depression. We fit models of progressive complexity, using Likelihood-ratio tests to assess whether each extra risk factor improved the fit of the model.

Model 1 Dialysis modality

. regress dt modality

```
      Source |       SS       df       MS      Number of obs   =       264
-------------+------------------------------   F(1, 266)       =     23.72
       Model |  171.013989     1  171.013989   Prob > F        =    0.0000
    Residual |  1918.09049   266  7.2108665   R-squared       =    0.0819
-------------+------------------------------   Adj R-squared   =    0.0784
       Total |  2089.10448   267  7.82436134   Root MSE        =    2.6853

------------------------------------------------------------------------------
          dt |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    modality |    1.598039   .3281445     4.87   0.000     .9519475    2.24413
       _cons |     2.51145   .2346162    10.70   0.000     2.049509    2.973392
------------------------------------------------------------------------------
```

Model 2 Gender

. regress dt gender

```
      Source |       SS       df       MS      Number of obs   =       264
-------------+------------------------------   F(1, 262)       =      5.25
       Model |  40.4393155     1  40.4393155   Prob > F        =    0.0228
    Residual |  2018.46599   262  7.70406865   R-squared       =    0.0196
-------------+------------------------------   Adj R-squared   =    0.0159
       Total |   2058.9053   263  7.82853727   Root MSE        =    2.7756

------------------------------------------------------------------------------
          dt |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      gender |   -.8376602   .3656167    -2.29   0.023    -1.557581    -.117739
       _cons |    3.882353   .3010583    12.90   0.000     3.289551    4.475155
------------------------------------------------------------------------------
```

Model 3 Depression

. regress dt depression

```
      Source |       SS       df       MS      Number of obs   =       264
-------------+------------------------------   F(1, 262)       =      4.45
       Model |  34.3541334     1  34.3541334   Prob > F        =    0.0359
    Residual |  2024.55117   262  7.72729454   R-squared       =    0.0167
-------------+------------------------------   Adj R-squared   =    0.0129
       Total |   2058.9053   263  7.82853727   Root MSE        =    2.7798

------------------------------------------------------------------------------
          dt |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  depression |    1.05117   .4985366     2.11   0.036     .0695213    2.032818
       _cons |   3.171053   .1840968    17.22   0.000     2.808555     3.53355
------------------------------------------------------------------------------
```

Model 4 Age^2

. regress dt age2

```
      Source |       SS       df       MS      Number of obs   =       264
-------------+------------------------------   F(1, 262)       =      5.91
       Model |  45.4001505     1  45.4001505   Prob > F        =    0.0157
    Residual |  2013.50515   262  7.68513417   R-squared       =    0.0221
-------------+------------------------------   Adj R-squared   =    0.0183
       Total |   2058.9053   263  7.82853727   Root MSE        =    2.7722

------------------------------------------------------------------------------
          dt |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        age2 |  -.0002111   .0000868    -2.43   0.016    -.0003821   -.0000401
       _cons |   4.247997   .4203016    10.11   0.000     3.420398    5.075596
------------------------------------------------------------------------------
```

Model 5 Dialysis modality plus gender

. regress dt modality gender

```
      Source |       SS       df       MS      Number of obs   =       264
-------------+------------------------------   F(2, 261)       =     17.46
       Model |  242.985705     2  121.492853   Prob > F        =    0.0000
    Residual |  1815.9196     261  6.95754635   R-squared       =    0.1180
-------------+------------------------------   Adj R-squared   =    0.1113
       Total |  2058.9053     263  7.82853727   Root MSE        =    2.6377

------------------------------------------------------------------------------
          dt |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    modality |    1.759202   .3260479     5.40   0.000     1.117183    2.401221
      gender |   -1.004504   .3488247    -2.88   0.004    -1.691373   -.3176351
       _cons |    3.095886   .3210922     9.64   0.000     2.463625    3.728147
------------------------------------------------------------------------------
```

LR test Model 5 (dialysis modality plus gender) vs Model 1 (modality alone)

Likelihood-ratio test — LR chi2(1) = 8.26

(Assumption: model1 nested in model5) — Prob > chi2 = 0.0041

LR test Model 5 (dialysis modality plus gender) vs Model 2 (gender alone)

Likelihood-ratio test — LR chi2(1) = 27.92

(Assumption: model2 nested in model5) — Prob > chi2 = 0.0000

So the model adjusting for dialysis modality plus gender is a better fit than the models adjusting for either modality or gender alone. Models 1 and 2 were therefore discarded.

Model 6 Dialysis modality plus gender plus depression

. regress dt modality gender depression

```
      Source |       SS       df       MS      Number of obs   =       264
-------------+------------------------------   F(3, 260)       =     12.84
       Model |  265.690396     3  88.5634652   Prob > F        =    0.0000
    Residual |  1793.21491   260  6.89698041   R-squared       =    0.1290
-------------+------------------------------   Adj R-squared   =    0.1190
       Total |   2058.9053   263  7.82853727   Root MSE        =    2.6262

------------------------------------------------------------------------------
          dt |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    modality |    1.734103   .3249203     5.34   0.000     1.094293    2.373914
      gender |   -.951364   .3485359    -2.73   0.007    -1.637676   -.2650516
  depression |     .85812   .4729549     1.81   0.071    -.0731897     1.78943
       _cons |   2.955674   .3288992     8.99   0.000     2.308029    3.603319
------------------------------------------------------------------------------
```

LR test Model 6 (dialysis modality plus gender plus depression) vs Model 3 (depression alone)

Likelihood-ratio test — LR chi2(2) = 32.03

(Assumption: model3 nested in model6) — Prob > chi2 = 0.0000

LR test Model 6 (dialysis modality plus gender plus depression) vs Model 5 (dialysis modality plus gender)

Likelihood-ratio test — LR chi2(1) = 3.32

(Assumption: model5 nested in model6) — Prob > chi2 = 0.0684

So the model adjusting for dialysis modality plus gender plus depression is a better fit than the model adjusting for depression alone, but not significantly better than the model adjusting for dialysis modality plus gender. Model 6 was therefore discarded.

Model 7 Dialysis modality plus gender plus age^2

. regress dt modality gender age2

```
      Source |       SS       df       MS      Number of obs   =       264
-------------+------------------------------   F(3, 260)       =     13.99
       Model |  286.074638     3  95.3582128   Prob > F        =    0.0000
    Residual |  1772.83066   260  6.81857948   R-squared       =    0.1389
-------------+------------------------------   Adj R-squared   =    0.1290
       Total |   2058.9053   263  7.82853727   Root MSE        =    2.6112

------------------------------------------------------------------------------
          dt |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    modality |    1.79353   .3230641     5.55   0.000     1.157375    2.429685
      gender |  -.8934869    .348136    -2.57   0.011    -1.579012   -.2079619
        age2 |  -.0002076   .0000826    -2.51   0.013    -.0003702    -.000045
       _cons |   3.921303   .4570064     8.58   0.000     3.021398    4.821208
------------------------------------------------------------------------------
```

LR test Model 7 vs Model 4

Likelihood-ratio test LR chi2(2) = 33.61
(Assumption: model4 nested in model7) Prob > chi2 = 0.0000

LR test Model 7 vs Model 5

Likelihood-ratio test LR chi2(1) = 6.34
(Assumption: model5 nested in model7) Prob > chi2 = 0.0118

So the model adjusting for dialysis modality plus gender plus age^2 is a better fit than the model adjusting for age^2 alone, and also somewhat better than the model adjusting for dialysis modality plus gender. Models 4 and 5 were therefore discarded in favour of model 7.

7.4 Discussion

7.4.1 Is there a difference in DT scores between CKD4/5 patients and haemodialysis patients?

We found that haemodialysis patients had significantly higher DT scores than CKD4/5 patients (median DT score 4 for haemodialysis patients and 2 for CKD4/5 patients, $p < 0.001$). This is in keeping with previous studies; Da Silva Gane[17] found that quality of life worsens after dialysis initiation, particularly in haemodialysis patients. In contrast, patients managed conservatively maintained their quality of life. There are many reasons why this should be the case. Kurella Tamura found that functional status declined following initiation of dialysis[101], while Carson[18] found that dialysis patients spent significantly more time in hospital compared with conservatively managed patients. There may also be an element of self-selection: patients with severe symptoms may be more likely to choose what they perceive to be an "active management" modality in the hope that their health may improve, where as those who feel well may be reluctant to "rock the boat" by starting dialysis.

7.4.2 What other factors affect DT scores?

Increasing age was associated with lower DT scores. This was unexpected – one might imagine that older patients would have more comorbidities and poorer functional status, and thus higher levels of distress. It may be that younger patients with CKD experience a greater dissonance between their own poor health and the good health of the majority of their peers (who may be travelling, having successful careers, and starting families – all of which are out of reach for young haemodialysis patients). In contrast, older CKD patients may "expect" poor health in old age, seeing this as a normal part of ageing.

Looking at the literature on distress in other diseases, Blank et al[323] and Cassileth et al[324] both report lower levels of distress in older cancer patients compared with younger ones, and Nelson et al[284]

specifically noted that DT scores were lower with increasing age in prostate cancer patients. They explained that "older adults, as compared with younger adults, demonstrate better emotion regulation, a more generative perspective, and a shifting of goals" (p897).

Female gender was also associated with increased distress (median DT score 4 compared with 2 for male patients, p = 0.027). It is not clear why this should be: are women more distressed in the general population, or is there something specific to CKD which affects women more than men? Or do women experience negative emotion as "distress" and men experience it as something else (such as anger, frustration)? Perhaps women are more willing to express their negative emotions – it must be remembered that this sample had a median age of 67 years old, and men of this generation were frequently encouraged to have a "stiff upper lip".

There was no association between DT scores and haemoglobin. This may be explained by the fact that patients in both cohorts will have their haemoglobin managed with erythropoietin therapy (either on dialysis or self-administered in the community), and this treatment should maintain haemoglobin within fairly tight limits. Indeed it is surprising that there was a difference in haemoglobin values between the two cohorts at all as both groups have the same treatment targets. The very low haemoglobin results seen in the study (Hb < 80g/L) may represent recent acute blood loss (such as from a bleeding fistula or duodenal ulcer) rather than chronic renal anaemia. Alternatively, the patients with very low haemoglobin results may not have engaged with Epo therapy, have contraindications to Epo therapy (such as uncontrolled hypertension), or may have inflammatory conditions (such as recent infection) which have made them Epo-resistant.

Low serum albumin is often a marker of poor overall physical health, and is associated with increased six-month mortality in CKD patients[44]. One might therefore hypothesise that patients with poor physical health would experience higher levels of distress. It is therefore rather surprising that low serum albumin does not appear to have a significant association with increased distress.

There was also no significant association between DT scores and either of the comorbidity indices (CCI and Davies score). Again this was an unexpected finding: we had hypothesised that patients with more comorbidities would be more distressed.

There was a weak negative association between eGFR and DT scores, which did not reach significance. There was also a weak negative association between distress and dialysis vintage – are patients with higher levels of distress more likely to die, or do patients get less distressed the longer they are on HD? It appears to be the latter, as there was no association between higher DT scores and one-year mortality.

Depression appears to be under-diagnosed in our cohort. Only 36 patients had a formal diagnosis of depression, compared with 97 patients who were "cases" on the HADS and 114 who were "cases" on the BDI-II. Under-diagnosis is well-recognised as a problem in the literature on depression in CKD patients[248,253,325], and screening for depression is often recommended for prevalent dialysis patients. Diagnosed depression does appear to be a risk factor for distress, whereas the other specific physical comorbidities that we looked at (diabetes, cardiovascular disease and peripheral vascular disease) were not.

In summary, the only significant risk factors for distress which we identified were: haemodialysis vs CKD4/5, younger age, female gender, and existing diagnosis of depression. It is notable that none of the physical risk factors examined were associated with increased DT scores. This points towards distress as a psychological phenomenon, although we demonstrated in Chapter 4 that distress is distinct from depression.

We then modelled the risk factors affecting DT score. The model which best fit our data was the model adjusting for age^2, gender and dialysis modality. Interestingly, the effect of an existing diagnosis of depression was attenuated once these other risk factors were accounted for, suggesting a degree of confounding (ie the differences in diagnosis of depression could be explained by differences in age, gender and dialysis modality).

One can easily imagine how age and gender might affect likelihood of diagnosis with depression (which, it must be remembered, is not the same as likelihood of *having* depression). It is interesting that dialysis is associated with higher rates of diagnosed depression, when (as discussed above) our data suggests that depression is under-diagnosed in this group. It is possible for both statements to be true: it seems that depression is diagnosed more frequently in dialysis patients than in CKD4/5 patients, but that this is still an under-representation of true rates of depression in this group.

7.4.3 **Limitations of the study**

There are potential issues regarding the timing of the administration of the questionnaires for dialysis patients. As previously discussed, most dialysis patients completed the questionnaires during dialysis sessions. It is known that patients' cognitive abilities are affected by dialysis ("brain stunning")[312]. It is also highly likely that patients experience heightened distress during dialysis sessions – they may experience pain (needling of fistulas, cramps), frustration (waiting for transport, machines not being ready), and anxiety (machines alarming). Further work needs to be done to examine whether distress does indeed change from baseline during dialysis sessions, as the higher rate of distress experienced by haemodialysis patients may be caused by dialysis itself, and may not be present on non-dialysis days.

Our sample size was well-powered to detect a difference in DT scores between CKD4/5 patients and HD patients, but may not have been sufficient to assess the effects of the less commonly-occurring risk factors (such as one-year mortality).

It appears that there was significant under-diagnosis of depression, which may have affected our estimation of the association between DT scores and depression. For example, if only the most severely-depressed patients are being diagnosed, this would tend to lead to an over-estimation of the relationship between distress and depression. This also raises the possibly of other co-

morbidities such as PVD and cardiac disease also being under-diagnosed, or at least under-recorded on the electronic patient record (EPR), again biasing our findings with respect to the association between DT scores and these comorbidities.

7.4.4 **Unanswered questions**

Some of the risk factors we examined, in particular eGFR and dialysis vintage, would be best assessed longitudinally. By following the trajectory of distress in the same patient, as eGFR declined or as they spent more time on dialysis, we would get a clearer picture of the effect of these risk factors on DT scores, controlled for individual confounders and inter-rater variability. We did not have enough repeated measures in this study to examine these risk factors longitudinally (due to high attrition rates), and our follow up period of two months was too short to see significant changes in eGFR in the CKD4/5 cohort, but we examine trajectories of distress in more detail in Chapter 8.

8 Distress Trajectory study

8.1 Introduction

8.2 Aim of this study

The first part of the study aims to examine change in DT scores in CKD4/5 patients, over a period of up to three years, and to assess whether change in DT scores is due to change in functional status or change in eGFR.

The second part of the study examines the six months before and after initiation of dialysis in more depth, and explores the trajectories of distress and functional status at this transitional time.

8.3 Part 1 Hypothesis

1. Higher DT scores are strongly associated with worse KPS scores and lower eGFRs.
2. Greater rise in DT scores over time (ie worse distress) is strongly associated with greater rate of decline in KPS scores and faster rate of decline in eGFR.

8.4 Part 2 Hypothesis:

1. DT scores worsen following initiation of haemodialysis, and do not return to baseline in the following six months

8.5 Methods

8.5.1 Research Ethics Committee approval

Research ethics committee approval was obtained from Health and Social Care 2 Research Ethics Committee of Northern Ireland (REC reference 13/NI/0075, see appendix A for approval letter).

8.5.2 Study group

8.5.3 Study Setting

The first part of this study was carried out at UCL Centre for Nephrology (CFN) Low Clearance Clinics (LCC) at the Royal Free Hospital (RFH), and its five satellite units. These clinics have approximately 1300 patients, and care is delivered by two nephrology consultants (0.5 WTE) and eight clinical nurse specialists (CNS). CFN policy is to transfer all renal patients to LCC clinic for management of their CKD symptoms and for dialysis modality planning when eGFR< 20mls/min (<30mls/min for diabetic patients). Conservatively managed (palliative) patients are also followed up in this clinic.

The second part of this study was carried out across the five satellite dialysis units managed by the Royal Free Hospital (RFH): Mary Rankin; Barnet; Edgware, St John and St Elizabeth, and Tottenham Hale (the Royal Free does not have any in-centre outpatient dialysis, only satellite outpatient units). Following the standard UK outpatient dialysis model, patients attend three times per week, for between 3-4.5hrs each, in one of six regular "slots" (either on Monday, Wednesday and Friday or Tuesday, Thursday and Saturday, in the morning, afternoon or evening).

8.5.4 Population

This study had two parts: the first used existing clinical data from the electronic patient record to assess change in distress scores over time in prevalent CKD patients. All patients aged 70 years or older, who attend CFN Low Clearance Clinics (LCC) at the Royal Free Hospital (RFH) or one of its five satellite units, were screened for eligibility for the study (approx. 900 patients).

Patients from within this cohort who started haemodialysis within the study recruitment period were approached for consent to participate in the second part of the study (change in distress around time of initiation of haemodialysis). Unfortunately due to the small size of the CFN's peritoneal dialysis cohort, a separate PD arm would not have been able to recruit enough patients to be adequately powered, and there is evidence that PD patients and HD patients are sufficiently

heterogenous[17] that a combined RRT arm would have been methodologically unsound. Patients who chose peritoneal dialysis were therefore excluded from the second part of the study.

8.5.5 Inclusion and Exclusion Criteria

8.5.5.1 Inclusion criteria for 1st part (prevalent CKD patients)

Attending CFN LCC clinics

Aged 70 years or older

At least three DT scores recorded on the electronic patient record (EPR)

8.5.5.2 Inclusion Criteria for 2nd part (change in distress around initiation of haemodialysis)

Took part in 1st part of study

Started haemodialysis within the last month

8.5.5.3 Exclusion Criteria (both parts)

Inability to consent

Unable to understand or complete Distress Thermometer (DT)

8.5.6 Sample size calculation

There were 921 patients >70yrs attending LCC on 01/10/2011. We assumed that, since the Distress Thermometer had been in routine use in LCC for over a year at that point, 50% of these patients would have at least three DT scores recorded in the EPR, and would thus be eligible for the first part of the study (giving a sample size of 460).

50-60 LCC patients >70yrs commence haemodialysis (HD) annually. We anticipated that at least 50 patients from the first part of the study would commence HD during the recruitment period (two years). Based on recruitment to previous studies, we felt that recruitment of 80% of eligible patients to part two of the study was realistic (based on the fact that the patient's regular team would be recruiting and consenting them, and that the study was not particularly burdensome).

8.5.7 Recruitment

8.5.7.1 Research team

The research team at the Royal Free comprised Helen Alston (HA); Aine Burns (AB), my supervisor and lead consultant for Low Clearance, who was study Primary Investigator (PI); and the Royal Free's Renal Systems and Clinical Data Manager (DW), who extracted the data for the 1st part of the study from the electronic patient record.

8.5.7.2 1st part: CKD

As only existing data from the electronic patient record (EPR) was used, and as this data was accessed only by HA (a member of the LCC clinical team) consent was not required. A list of potentially eligible patients was obtained from the EPR, and this was manually searched to produce a list of eligible patients. A database query was then run by our Renal Systems and Clinical Data Manager to extract the data needed for analysis from the EPR.

8.5.7.3 2nd part: Initiation of haemodialysis

Eligible patients were identified by HA by cross-referencing the monthly renal modality report (this is a routinely generated database query which lists patients who have changed from "low clearance"

to “haemodialysis” on our renal database) with the EPR to confirm that they met the other inclusion criteria. Eligible patients were then approached in the dialysis unit on arrival for their routine dialysis session, and asked if they were interested in taking part. If they expressed interest, they were provided with a written patient information leaflet, and given time to consider the study and to ask questions. Those who were happy to proceed were asked to provide written consent. Patients who refused were not approached again.

8.5.8 **Data**

Outcomes of interest: Change in distress thermometer scores over time

Risk factors of interest: Residual renal function measured by eGFR (MDRD), planned treatment modality (low clearance, dialysis, conservative care), biochemical and haematological parameters, co-morbidities, functional status (routinely recorded by KPS scoring at each visit) and demographic data (age, sex, ethnicity, etc).

8.5.8.1 Data Collection

Data for part one of the study was collected retrospectively from the electronic patient record.

The distress thermometer is not routinely used in our dialysis units, so for part two of the study, HA administered the DT monthly (on the same day of the week each time, to minimise the potential for fluctuations in distress scores caused by changes in biochemical/fluid status related to dialysis). If the patient did not attend their regular session, HA attended the next session that they were expected at or, where this was not possible, the corresponding session the following week. The data for other risk factors was obtained from the electronic patient record.

8.5.8.2 Data handling and record keeping

Names, hospital numbers, dates of birth and genders of patients, along with data relating to the outcomes of interest listed above, was collected from the electronic patient record in accordance with the patient consent form, patient information sheet and the study protocol. This data was manually inputted into a spreadsheet using Excel 2010 (Microsoft) and sent electronically to HA for statistical analysis using the statistical package STATA/IC 12.1 (StataCorp LP). University College London acted as the data controller for the study.

HA processed, stored and disposed of the patient demographic information and in accordance with all applicable legal and regulatory requirements, including the Data Protection Act 1998. Patient data was stored centrally at the Centre for Nephrology as follows: the hard copies of questionnaires were stored in a locked filing cabinet controlled by HA, and the database was stored on password-protected UCL computers in a secure office (requiring swipecard access), and on an NHS-issued encrypted USB stick (for transfer between NHS sites only).

8.5.9 Statistical Methods

8.5.9.1 Part 1

Data was analysed using STATA/IC 12.1 (StataCorp LP). Linear regression was used to analyse distress and KPS at baseline. Multi-level regression was used to look at changes of distress and KPS score over time, adjusted for eGFR and the factors previously shown in our model to be significantly associated with higher DT scores (age and gender – all patients in Part One were CKD4/5 so their modality was the same) (see Chapter 6 for further information on multi-level models).

8.5.9.2 Part 2

We originally intended to model the change in trajectory in DT scores following initiation of dialysis using multiple regression analysis. However, in the event of low recruitment we instead used a technique previously used by Murtagh et al[326] to assess trajectories of illness in CKD5: Visual Graphic Analysis. Described by Brown et al[327], Visual Graphic Analysis (VGA) is a qualitative method of assessing trajectories by visual inspection.

Individual trajectories were plotted using Stata. Time was centred around date of first dialysis session. Graphs were plotted using the same scales, and also using the same colours and layout to avoid any inadvertent visual biases. The graphs were compared, and common patterns identified. These patterns were then verified by a second researcher. Where there was any disagreement this was discussed until agreement was reached.

8.5.10 **Missing data**

If data was missing we treated this as "data missing completely at random", as this was felt likely to be due to factors such as nursing staff forgetting to enter the data, distress thermometers being taken home instead of being handed in, etc. Maximum likelihood estimations were used in imputation. Refusal to complete DTs is documented as a separate category in the EPR (this would be data missing not at random), and this data was therefore not imputed.

8.5.11 **Withdrawal from study**

As part one of the study was a retrospective review of anonymised, routinely-collected clinical data, patient consent was not required and therefore patient withdrawal was not an issue.

If patients in part two withdrew their consent to take part in the study, they were asked if they gave consent for continued use of the data already collected. If they said yes, we continued to use this data. If they said no, all of their data was removed from the study. Consent and capacity were confirmed with the patient monthly while the patient remained in the study, immediately prior to the administration of the DT.

8.5.12 Ethical Considerations

Ethics committee approval was obtained from Research Ethics Committee as previously discussed (see Appendix A). There were few ethical considerations for part one of the study, as this was retrospective analysis of routinely-recorded data. For part two, if any patients expressed high levels of distress or suicidal ideation, this was immediately communicated to the patients named nurse and dialysis consultant for further action.

8.6 Part 1 Results

8.6.1 Sample size

We obtained records for 316 CKD4/5 patients aged over 70 who had three or more completed DTs recorded on the electronic patient record. Baseline characteristics are shown in table.

8.6.2 Statistical analysis

We carried out a simple linear regression to confirm that our previous findings were also valid in this new cohort (ie that age and gender affected DT scores while eGFR did not), and to assess the impact of low functional status using the Karnofsky Performance Scale on DT scores.

We then carried out a multi-level regression to assess how DT score changed over time with eGFR and KPS scores.

8.6.3 Baseline characteristics of the sample (n=318)

The mean age was 85, and 64% of the participants were male. On average there were 5 recorded DT scores on the EPR, however some patients had up to 16 DT scores recorded. eGFRs ranged from 54mls/min down to 7mls/min (mean not calculated, as different participants have multiple measurements of renal function included in the study data).

Table 8.1 Baseline characteristics of CKD4/5 cohort

	Mean (min/max values)
Age	85.2 years (min 72.78 - max 104.54)
Gender	64% male
Number of DTs recorded	5 (3 – 16)
eGFR range	7 – 54 mls/min

8.6.4 Linear regression

We next carried out linear regression to confirm that the variable previously found to be associated with DT scores in the cross-sectional study (Chapter 7) were also significant in this cohort.

8.6.4.1 Age

. regress distressscore age

```
      Source |       SS       df       MS              Number of obs =    1547
-------------+------------------------------           F(  1,  1545) =    2.58
       Model |  21.9059849     1  21.9059849            Prob > F      =  0.1085
```

```
   Residual |  13125.5497  1545  8.49550145         R-squared     =  0.0017
-------------+----------------------------         Adj R-squared =  0.0010
     Total |  13147.4557  1546  8.50417576         Root MSE      =  2.9147

------------------------------------------------------------------------------
distresssc~e |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       age |   .0179742   .0111934     1.61   0.109    -.0039817    .0399301
     _cons |   .9844541   .9103949     1.08   0.280     -.801286    2.770194
------------------------------------------------------------------------------
```

Interestingly, increasing age is associated with increasing DT scores in this cohort (not statistically significant, p=0.109). It must be noted that this cohort only includes patients older than 70 years, while the cohort in Chapter 7 included all age groups.

8.6.4.2 Sex

```
. regress distressscore Sex

      Source |       SS       df       MS              Number of obs =    1547
-------------+------------------------------           F(  1,  1545) =    5.04
       Model |  42.7174505     1  42.7174505           Prob > F      =  0.0250
    Residual |  13104.7383  1545  8.48203124           R-squared     =  0.0032
-------------+------------------------------           Adj R-squared =  0.0026
       Total |  13147.4557  1546  8.50417576           Root MSE      =  2.9124

------------------------------------------------------------------------------
distresssc~e |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         Sex |   .3504643   .1561676     2.24   0.025     .0441414    .6567872
       _cons |   2.321884   .0912353    25.45   0.000     2.142926    2.500842
------------------------------------------------------------------------------
```

Female gender remains associated with higher DT scores in this cohort (p=0.25)

8.6.4.3 Karnofsky Performance Scale

```
. regress distressscore karnscore

      Source |       SS       df       MS              Number of obs =     778
-------------+------------------------------           F(  1,   776) =   89.25
       Model |  703.768357     1  703.768357            Prob > F      =  0.0000
    Residual |  6118.98357   776  7.88528811           R-squared     =  0.1032
-------------+------------------------------           Adj R-squared =  0.1020
       Total |  6822.75193   777  8.78089051           Root MSE      =  2.8081

------------------------------------------------------------------------------
distresssc~e |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   karnscore |  -.0570595   .0060398    -9.45   0.000    -.0689157   -.0452032
       _cons |   6.731523   .4519192    14.90   0.000     5.844394    7.618652
------------------------------------------------------------------------------
```

There is a significant negative association between KPS scores and DT scores – ie the lower the KPS (worse functional status), the higher the level of distress is likely to be ($p<0.001$).

8.6.4.4 eGFR

```
. regress distressscore eGFR

      Source |       SS       df       MS              Number of obs =    1534
-------------+------------------------------           F(  1,  1532) =    0.08
       Model |  .661553143     1  .661553143           Prob > F      =  0.7803
    Residual |  13024.1885  1532  8.50142853           R-squared     =  0.0001
-------------+------------------------------           Adj R-squared = -0.0006
       Total |  13024.8501  1533  8.49631446           Root MSE      =  2.9157

------------------------------------------------------------------------------
distresssc~e |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       eGFR |   .0025448   .0091226     0.28   0.780    -.0153492    .0204388
      _cons |   2.383222   .1971893    12.09   0.000     1.996433    2.770012
------------------------------------------------------------------------------
```

There is no association between eGFR and DT score in this linear model (p=0.780)

8.6.5 **Multi-level modelling**

We then fitted a multi-level model to assess how DT scores were affected by KPS scores over time:

8.6.5.1 Model 1 - KPS

. xtmixed distressscore karnscore || patHospNo1 :

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0: log likelihood = -1816.5378
Iteration 1: log likelihood = -1816.5378

Computing standard errors:

Mixed-effects ML regression Number of obs = 778
Group variable: patHospNo1 Number of groups = 259

Obs per group: min = 1
avg = 3.0
max = 9

Wald chi2(1) = 43.48
Log likelihood = -1816.5378 Prob > chi2 = 0.0000

distressscore	Coef.	Std. Err.	z	P>|z|	[95% Conf. Interval]	
karnscore	-.0478348	.0072543	-6.59	0.000	-.0620529	-.0336167
_cons	6.066753	.5499417	11.03	0.000	4.988887	7.144619

```
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
patHospNo1: Identity         |
                sd(_cons) |   1.942827   .1243983      1.713689    2.202602
-----------------------------+------------------------------------------------
             sd(Residual) |   2.030001   .0626223       1.9109    2.156525
------------------------------------------------------------------------------
LR test vs. linear regression: chibar2(01) =   179.36 Prob >= chibar2 = 0.0000

. estat icc

Residual intraclass correlation

------------------------------------------------------------------------------
                   Level |       ICC   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
               patHospNo1 |   .4780679   .0381136      .4043998    .5527026
------------------------------------------------------------------------------
```

This confirmed that KPS is strongly associated with DT scores ($p<0.001$). ICC was estimated at 0.478 (95% CI 0.404 – 0.553), suggesting that 47.8% of variation in the relationship between DT and KPS is actually due to individual differences between participants.

8.6.5.2 Model 2 – KPS and age

```
. xtmixed distressscore karnscore age || patHospNo1 :

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -1816.1284
Iteration 1:   log likelihood = -1816.1284

Computing standard errors:

Mixed-effects ML regression                    Number of obs      =       778
Group variable: patHospNo1                     Number of groups   =       259

                                               Obs per group: min =         1
                                                             avg =       3.0
                                                             max =         9


                                               Wald chi2(2)       =     44.40
Log likelihood = -1816.1284                    Prob > chi2        =    0.0000

------------------------------------------------------------------------------
distressscore |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
   karnscore |  -.0497178   .0075366    -6.60   0.000    -.0644892   -.0349464
         age |  -.0198916    .021968    -0.91   0.365    -.0629482    .0231649
       _cons |   7.820604   2.012497     3.89   0.000     3.876182    11.76503
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
```

```
patHospNo1: Identity         |
               sd(_cons) |   1.938808   .1242011      1.71004     2.19818
-----------------------------+------------------------------------------------
            sd(Residual) |   2.029869   .0625994     1.910811    2.156346
------------------------------------------------------------------------------
LR test vs. linear regression: chibar2(01) =   178.53 Prob >= chibar2 = 0.0000
```

```
. lrtest M2 M1

Likelihood-ratio test                           LR chi2(1)  =      0.82
(Assumption: M1 nested in M2)                   Prob > chi2 =    0.3655
```

As might have been expected from the linear regression, the addition of age to the model does not improve its fit (LR test p=0.3655). We therefore discarded Model 2.

8.6.5.3 Model 3 – KPS and Sex

```
. xtmixed distressscore karnscore Sex || patHospNo1 :

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log likelihood = -1814.6427
Iteration 1:   log likelihood = -1814.6427

Computing standard errors:

Mixed-effects ML regression                     Number of obs      =       778
Group variable: patHospNo1                      Number of groups   =       259

                                                Obs per group: min =         1
                                                               avg =       3.0
```

```
                                        max =        9


                                  Wald chi2(2)      =     47.68
Log likelihood = -1814.6427               Prob > chi2       =     0.0000

------------------------------------------------------------------------------
distressscore |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
   karnscore |  -.0461927   .0072782    -6.35   0.000    -.0604577   -.0319277
         Sex |   .5941945   .3045475     1.95   0.051    -.0027076    1.191097
       _cons |   5.737702   .5735642    10.00   0.000     4.613537    6.861867
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
patHospNo1: Identity         |
               sd(_cons) |   1.928413   .1235771      1.700799    2.186487
-----------------------------+------------------------------------------------
            sd(Residual) |   2.028091   .0624842      1.909248    2.154331
------------------------------------------------------------------------------
LR test vs. linear regression: chibar2(01) =   178.51 Prob >= chibar2 = 0.0000

. estimate store M3

. lrtest M3 M1

Likelihood-ratio test                           LR chi2(1)  =      3.79
(Assumption: M1 nested in M3)                   Prob > chi2 =    0.0516
```

Again, the addition of Sex to the model did not improve the fit (LR test p=0.0516). Model 3 was therefore discarded.

8.6.5.4 Model 4 – KPS and eGFR

```
. xtmixed distressscore karnscore eGFR || patHospNo1 :

Performing EM optimization:

Performing gradient-based optimization:

Iteration 0:   log likelihood =  -1797.624
Iteration 1:   log likelihood =  -1797.624

Computing standard errors:

Mixed-effects ML regression                 Number of obs     =       771
Group variable: patHospNo1                  Number of groups  =       257

                                            Obs per group: min =         1
                                                          avg =       3.0
                                                          max =         9


                                            Wald chi2(2)      =     41.31
Log likelihood =  -1797.624                 Prob > chi2       =    0.0000

------------------------------------------------------------------------------
distressscore |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
   karnscore |  -.0465006   .0072781    -6.39   0.000    -.0607654   -.0322359
       eGFR |   -.008406   .0147109    -0.57   0.568    -.0372388    .0204268
      _cons |   6.154651   .6231799     9.88   0.000     4.93324    7.376061
------------------------------------------------------------------------------

------------------------------------------------------------------------------
 Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
----------------------------+-------------------------------------------------
```

```
patHospNo1: Identity        |
              sd(_cons) |   1.959657   .1259351      1.727741    2.222703
------------------------------+------------------------------------------------
           sd(Residual) |    2.01546   .0627113      1.896221    2.142198
------------------------------------------------------------------------------
LR test vs. linear regression: chibar2(01) =   179.79 Prob >= chibar2 = 0.0000
```

```
. estimate store M4
. lrtest M4 M1
```

```
Likelihood-ratio test                     LR chi2(1)  =      0.33
(Assumption: M1 nested in M4)             Prob > chi2 =    0.5684
```

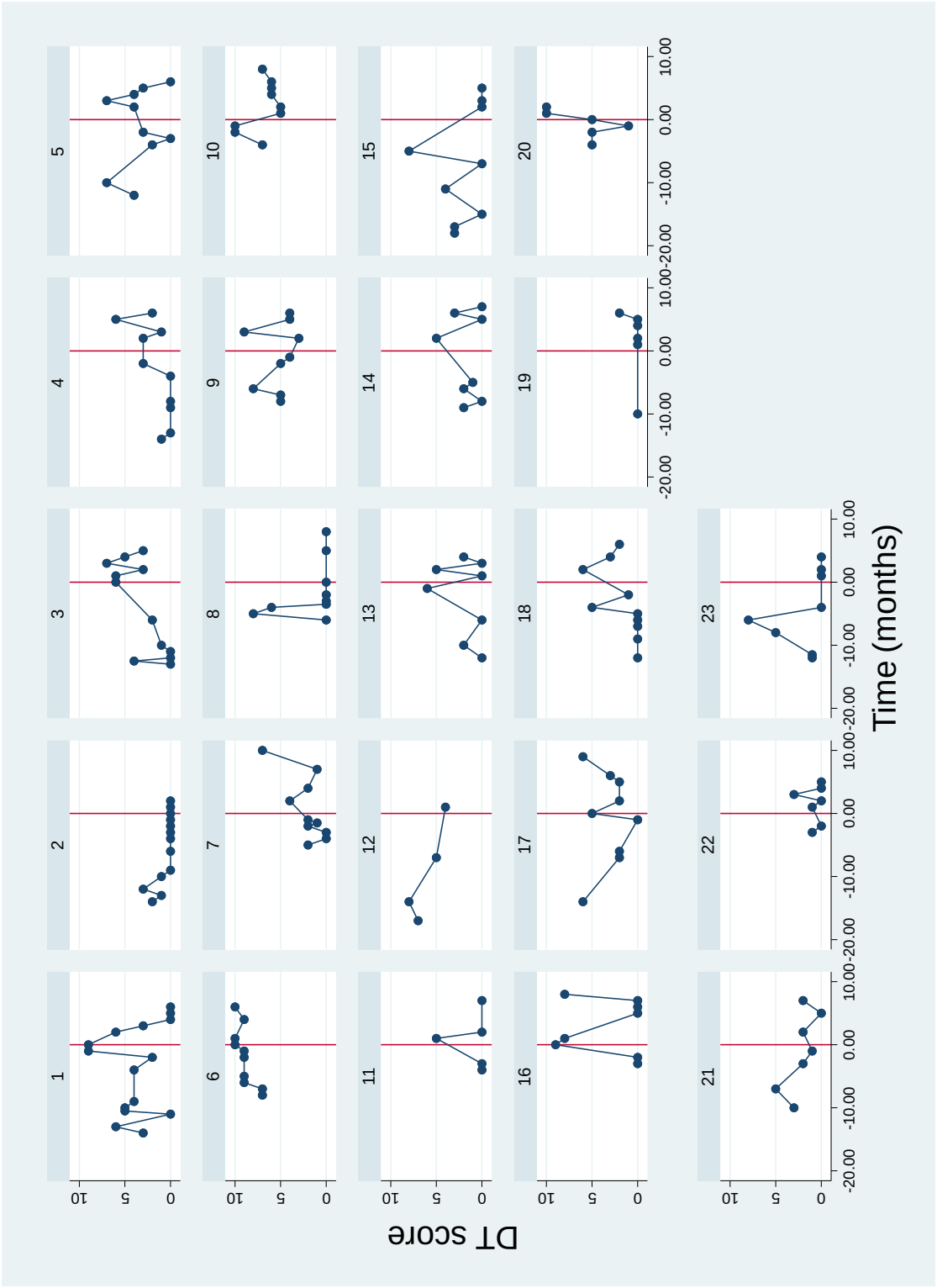
The addition of eGFR to the model did not improve the fit (LR test p=0.5684). Model 4 was also discarded.

Model 1, adjusting simply for KPS scores and for clustering at the individual level, provides the best fit for the data. There was a moderately large amount of variability at the level of the individual (47.8%).

8.7 Part 2 Results

8.7.1 Visual Graphical Analysis

Figure 8.8.1 DT trajectories around start of dialysis



We identified five categories of trajectory of DT scores: flat trajectory (divided into flat low and flat high), rising at start of dialysis but returning to baseline, rising at start of dialysis but not returning to baseline, and other rises in DT score.

8.7.2 **Category 1: Flat trajectory, low distress**

Figure 8.8.2 DT trajectories - flat progression

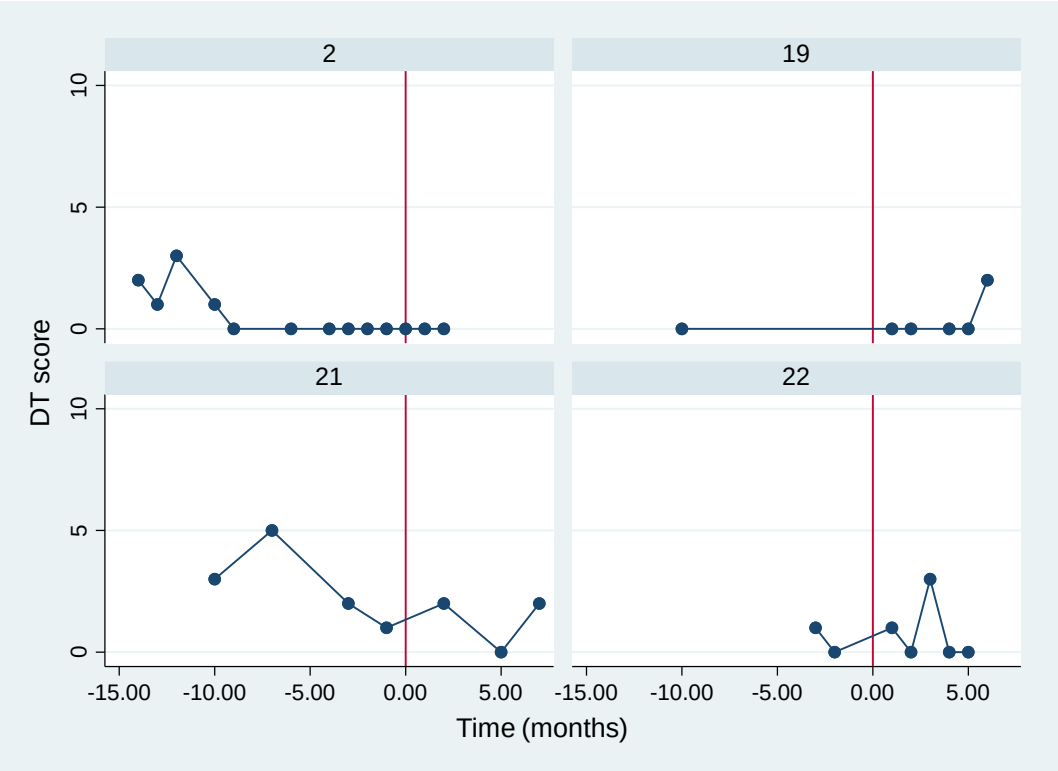
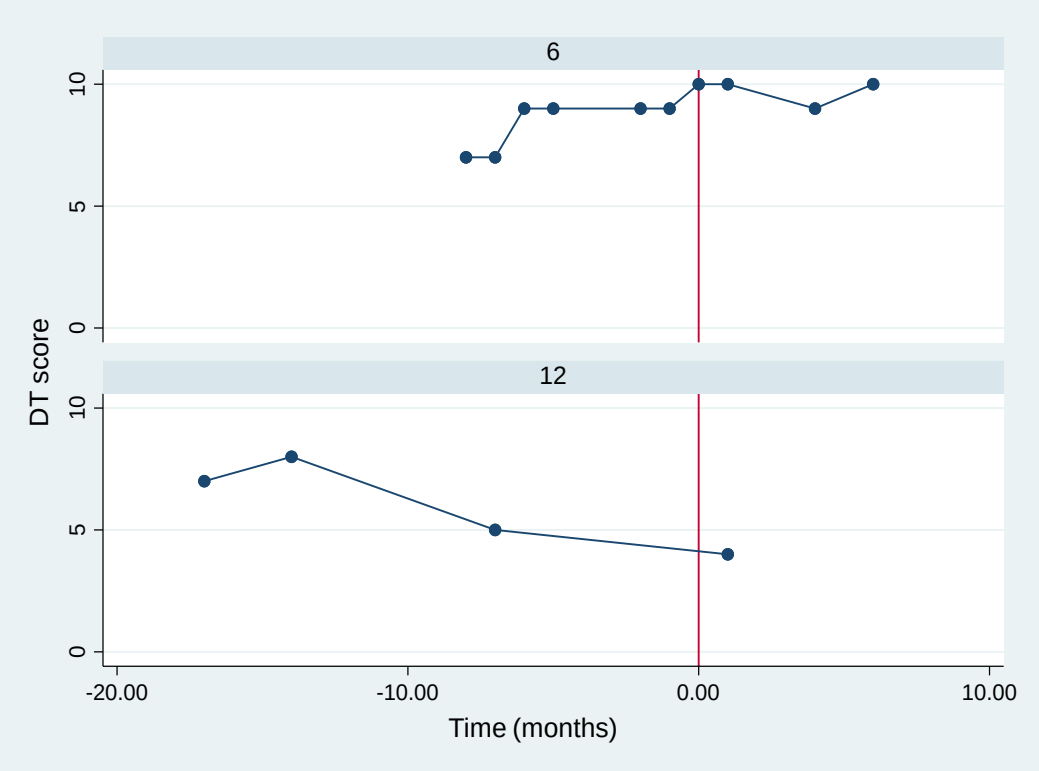


Figure 8.8.2 shows the four participants with a flat, low distress trajectory. Their pre-dialysis DT scores were low, and there is no rise around the time of start of dialysis.

These participants may genuinely not be upset by the transition onto dialysis, or they may simply not identify with the concept of distress or wish to discuss this with their healthcare providers.

8.7.3 **Category 2: Flat trajectory, high distress**

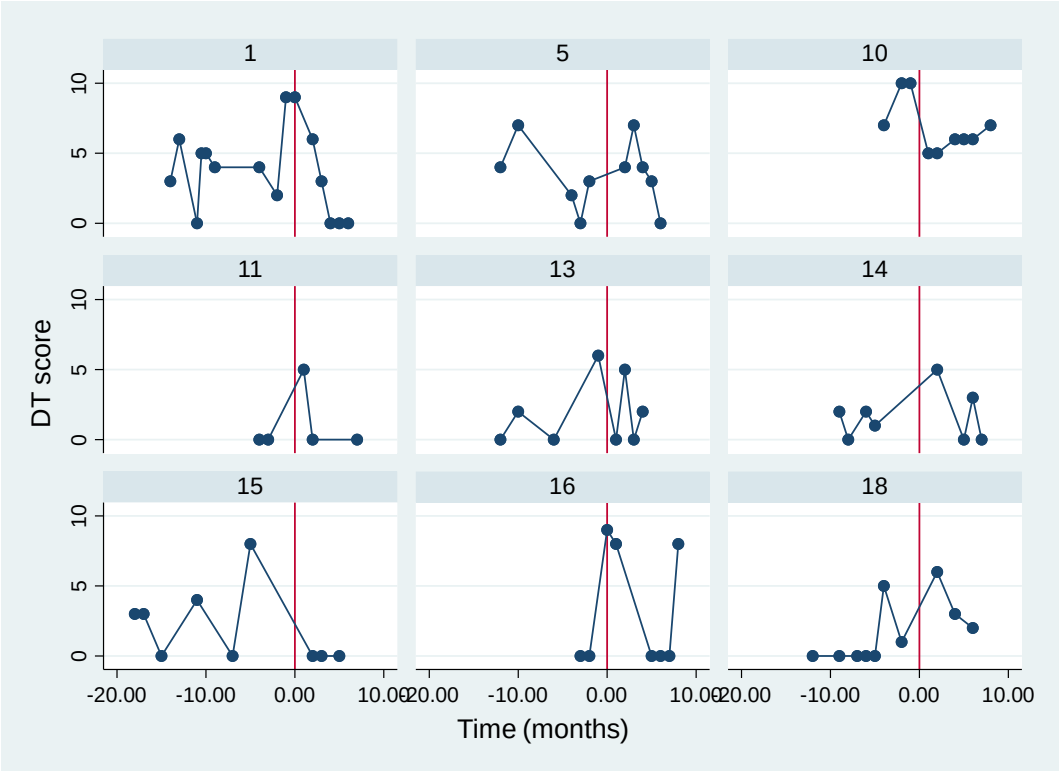
Figure 8.8.3 DT trajectories - always high



These two participants had high levels of distress (DT score >6) in the pre-dialysis stage. There is no noticeable change in their DT scores around the time of starting dialysis, but their scores do not improve either. It is possible that the cause of their distress is unrelated to their medical situation.

8.7.4 **Category 3: Rising but resolving**

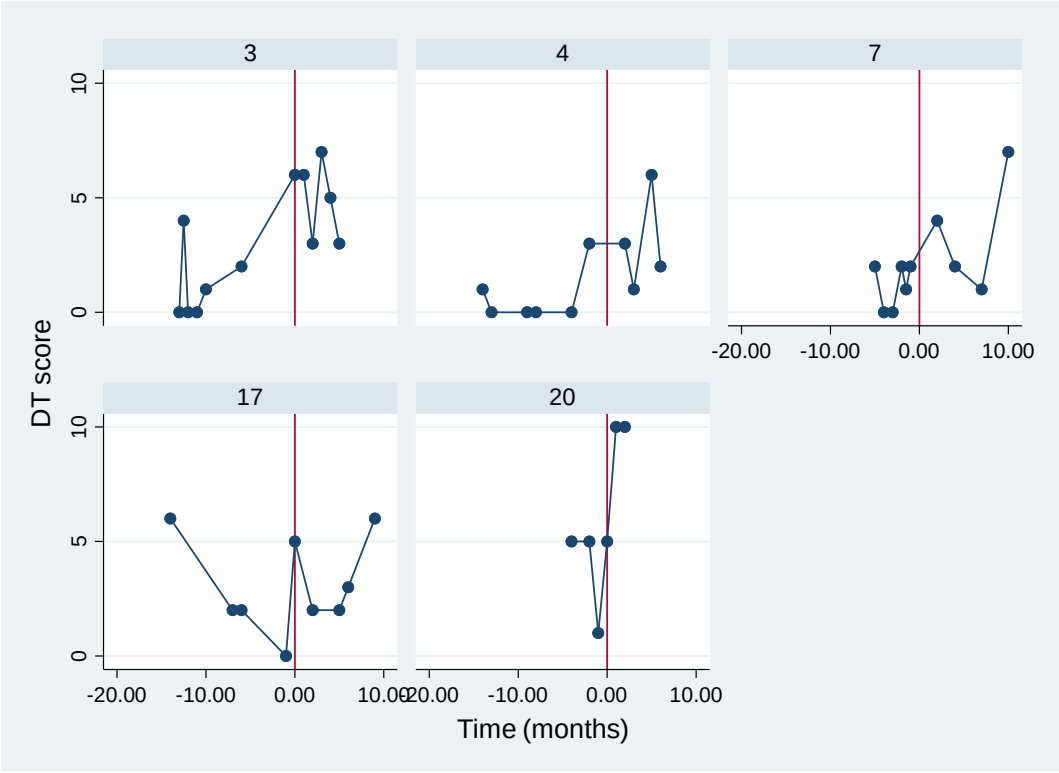
Figure 8.8.4 DT trajectories - rising then resolving



In this category, participants had an obvious rise in their DT score around the time of starting dialysis, but this returned to baseline within a few months. Some of these participants had other rises in their DT score at other times (for example, participant 5 had a substantial rise in his DT score approximately 10 months before starting dialysis) – it is unknown what caused this rise.

8.7.5 **Category 4: Rising but not resolving**

Figure 8.8.5 DT trajectories - rising but not resolving

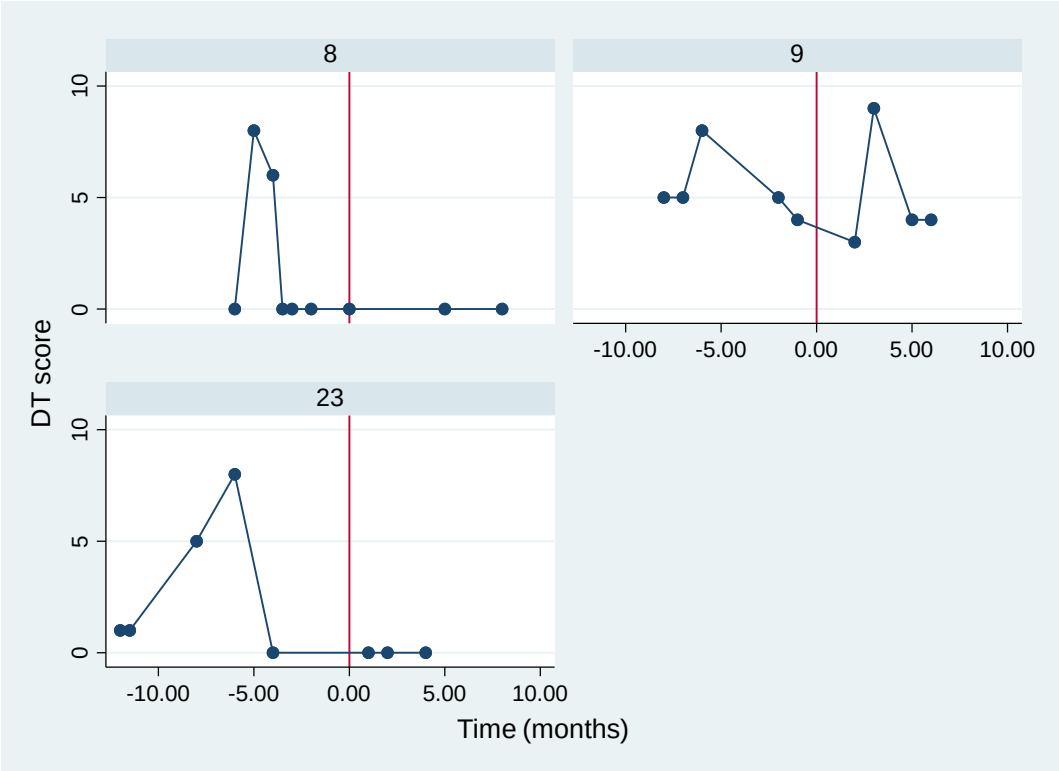


These participants also had a substantial rise in their DT scores around the time of start of dialysis, but unlike those in category 3, there was no return to baseline observed.

In some cases, such as participant 20, this may be because follow up was curtailed (by patient death, in that particular case). In others, such as participants 7 and 17, there is a slight improvement followed by another rise. It may be that the second rise is unrelated to dialysis, as in both instances it occurred over six months after starting dialysis.

8.7.6 **Category 5: Other patterns**

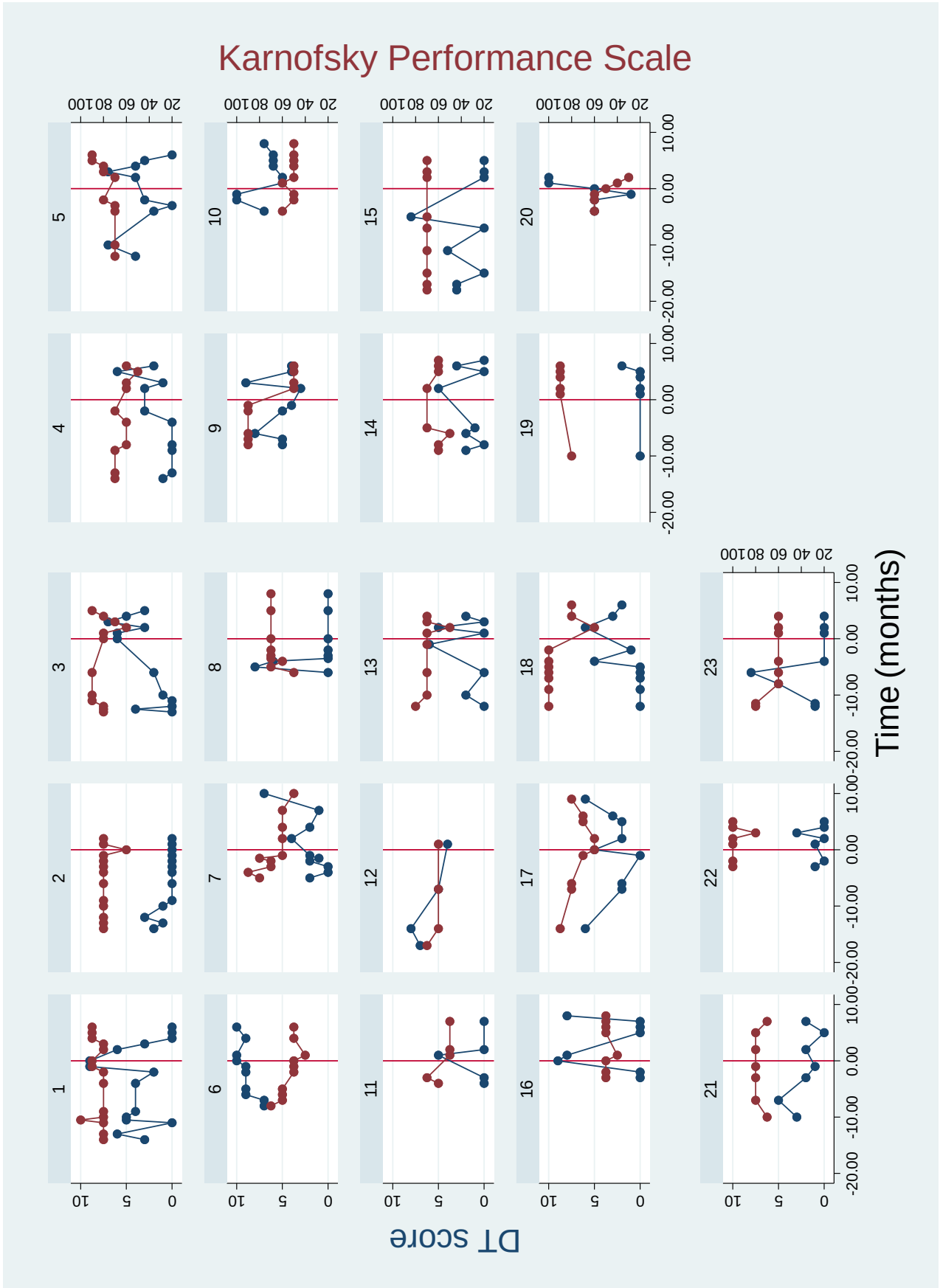
Figure 8.8.6 DT trajectories - other patterns



These participants did not fit into any of the previous patters. Participants 8 and 23 have large rises six months prior to starting dialysis, but then a flat trajectory around the initiation of dialysis and in the time after that. It would be interesting to know whether this coincided with a hospital admission, bereavement, or other major life event.

Participant 9 has several smaller rises in DT score, but neither seems to be temporally related to starting dialysis.

Figure 8.8.7 DT and KPS trajectories around start of dialysis



8.7.7 **Comparing trajectories of KPS and DT**

Figure 8.8.7 plots the trajectories of DT and KPS for the year before and after starting dialysis (time is centred on date of first dialysis session).

It is apparent that high KPS scores are associated with lower DT scores, and vice versa. However the DT appears to be much more variable than the KPS – KPS scores change gradually and slowly, while the DT can go up and down fairly rapidly.

Equally, DT scores often worsen but then improve again quite rapidly. In contrast, a decline in KPS of more than 10% (which may be due to inter-reporter variability) does not seem to improve.

8.8 Discussion

8.8.1 Part One

The relationship between the DT and KPS is strong. For each 10% loss of functional independence on the KPS, DT score falls by 0.47 ($p<0.001$). This relationship is moderately stable over time – up to 47.8% of the variability in this relationship is due to variation at the level of the individual. Interestingly in Chapter 6 we did not find a particularly strong association between the SF-36 Physical Functioning subscale and DT scores – this may because the SF-36 does not discriminate well between lower levels of physical functioning (there is a "floor" effect) and so almost all of our patients had low scores on that particular subscale.

The relationship between DT scores and other factors, such as gender, eGFR and age, is much less strong. We have an age-restricted sample, which may explain why age is not a significant risk factor for increased distress. However it is surprising that falling eGFR does not have an impact on distress. The participants were followed for up to three years, and in that time we recorded eGFRs as low as 7mls/min, which is certainly low enough to expect participants to have experienced some uraemic symptoms.

8.8.2 Part Two

We identified five categories of DT trajectory. The majority of participants showed an increase in distress around the time of starting dialysis, however while some returned to baseline (adapted) after a couple of months, not everybody did.

A minority were unaffected by the start of dialysis – either because they reported no distress at all (category 1), which might suggest that they would use a different word to describe their negative emotions, or because they were so distressed all the time that dialysis made no difference to their

DT scores (category 2). Both of these categories of participants should be probed gently by the clinical team to ensure that they are receiving all the help that they wish to receive.

A final category did not experience a rise in distress around the time of start of dialysis but did experience a rise in distress at other times. The causes of these non-dialysis rises are not known.

8.8.3 **Clinical implications**

How do we reconcile the findings of Part One and Part Two? Low eGFR is not associated with higher levels of distress, however in Part Two we found that the majority of participants experience a rise in DT scores around the time of start of dialysis, and for some participants this rise does not return to baseline even after six months. The distressing aspects of dialysis appear to be unrelated to prosaic changes in eGFR – this aspect needs to be explored in more detail, but from a clinical perspective, the exhortation to "treat the patient, not the figures" should be born in mind.

On the other hand, poor functional status (low KPS scores) do seem to be associated with higher levels of distress. Kurella Tamura[101] noted a functional decline around time of initiation of dialysis, and this did not recover to baseline even after several months. There are a number of studies examining the efficacy of physical rehabilitation for renal patients[115,119,328] – functional decline is however very difficult to reverse, even with very motivated patients. Patients suffering from distress may be in no position to engage with physiotherapy.

8.8.4 **Limitations of this study**

The very small numbers recruited to Part Two meant that we were unable to carry out a regression analysis to assess which factors are associated with more unfavourable trajectories. We were able to carry out a Visual Graphical Analysis, but this is an exploratory technique without the ability to assess risk factors of interest.

8.8.5 **Unanswered questions**

We need to do further work to investigate which patients' DT scores do not return to baseline following initiation of dialysis, and why that might be. It would also be extremely interesting to know what causes the rises in DT scores which are not associated with starting dialysis (category 5) – are the causes related to other health matters, or not related to health at all?

9 Qualitative Study

9.1 Introduction

9.2 Aims

To explore factors affecting distress in an older UK adult renal population (CKD 4/5, aged over 70 years).

9.3 Specific research questions

1. How do patients define distress?
2. What are the causes of distress in CKD4/5 and dialysis patients?
3. What do we as healthcare professionals currently do, and what could we do differently, to mitigate this distress?

9.4 Research Ethics Committee Approval

Research Ethic Committee approval was obtained from West of Scotland Research Ethics Committee 5 (ref 14/WS/0120, see Appendix A for approval letter).

9.5 Methodology

I have chosen to use an interpretative (hermeneutic) phenomenological approach. I believe that the appropriate object of study for this project is the global phenomenon of distress, rather than the conscious attitudes of patients towards their own distress. Spiegelberg described hermeneutics as "the attempt to grasp the essential structures of the phenomena, and the essential relationships within and among them" p62 [329].

The phenomenon of distress is likely to be different for patients who have not yet started dialysis (who may be apprehensive about dialysis in the future) compared with patients who are already on dialysis (who have direct lived experience of dialysis). For this reason I will interview participants from both of these different stakeholder groups.

I have chosen an interpretative rather than descriptive phenomenological approach because, as a nephrologist myself, I recognise the limitations of my own subjectivity. The interpretative approach effectively utilises my pre-existing expert knowledge and facilitates a co-constitution between researcher and participant.

In contrast, a descriptive approach would require a "bracketing", or examination and conscious rejection, of my prior personal knowledge in order to truly understand the participants' perspective [330,331]. In this particular context, I would find this inauthentic; my position as a nephrologist is precisely what has driven my interest in this research topic, an aspect which Koch acknowledges [331]. It is also unlikely that participants, who already know that I am a healthcare professional, would be able to set this knowledge aside. This power imbalance is something that I was very aware of during the interviews, and although I took steps to mitigate it (by encouraging frank opinions from the participants, mirroring them when they expressed their opinions of other healthcare professionals, and stressing the confidential nature of the interview), it is likely that it still influenced the interviews overall.

The concept of the "Hermeneutic Circle", from theologian Schleiermacher [332], describes the process by which, in interpretative phenomenology, the researcher's position in the world affects their interpretation of the data, which then prompts reflection and synthesis, and the generation of new knowledge. This process may be facilitated by the use of a reflexive journal (or contemporaneous notes on the interview process), which I have used in the past to good effect.

In terms of evaluation of the study, Heideggerian scholars would reject the concept of external validity, since knowledge is viewed through the lens of a person's previous experience, and is never

independent of interpretation[333,334]. Instead, Koch suggests that a piece of interpretative phenomenological research should be judged on the criteria of *philosophy* (the research should demonstrate a clear understanding of the philosophical underpinnings of the methodology), *representation* (a clear process of reflection on the part of the researcher, and co-constitution between researcher and participant) and *rigor* (which Koch describes as a clear explication of the way in which the research was carried out, with justification for research decisions made)[333].

In broader terms, Merriam and Patton have both produced useful frameworks for evaluating qualitative research in general [299,335], which I have referred to when preparing this chapter.

9.6 Methods

9.6.1 Study Design

Semi-structured interviews with older renal patients: patients were purposively selected to include a broad range of gender, socio-economic class, ethnic group and experience of nephrology services.

9.6.2 Study group

9.6.2.1 Population

All patients aged 70 years or older attending UCL Centre for Nephrology (CFN) Low Clearance Clinics (LCC) at the Royal Free Hospital (RFH) and its 5 satellite units (approx. 1300 patients). CFN policy is to transfer all renal patients to LCC clinic when eGFR< 20 for non-diabetic and <30 for diabetic patients. Care is delivered by 2 consultants (0.5 WTE) and 8 clinical nurse specialists (CNS).

9.6.2.2 Inclusion Criteria

1. Attending CFN low clearance clinics or dialysis units
2. Aged 70 years or older

9.6.2.3 Exclusion Criteria

1. Inability to consent
2. Unable to comprehend spoken english (as we were carrying out a content analysis, validity would be affected if translation services were used).
3. Change in modality in last three months (likely to lead to confusion about whether sources of distress relate to old or current modality, hard for patient to assess new modality accurately)

9.6.3 **Recruitment**

Eligible patients from each of four treatment modalities (LCC, HD, PD, CM) were identified by the research team from the renal patient database, in discussion with the renal multidisciplinary team (who have personal knowledge of the patients and can therefore assess suitability for the study). Patients were purposively selected to represent our elderly LCC population (age, sex, ethnicity, social, functional and carer status), enriched by inclusion of patients with particularly high or low DT scores in the past.

The patient information sheet and a covering letter were sent to all eligible patients. Patients were then asked by a member of the team at their next routine appointment whether they were interested in taking part in the study. If they expressed interest, a member of the research team provided them with written information about the study, and they were given time to consider the study and to ask questions.

Those who were happy to proceed were asked to provide written consent, and an appointment was made for the researcher to carry out the interview. A phone call was made to the patient the day before this appointment to confirm that they were still happy to proceed. Patients who refused were not approached again.

9.6.4 Data

9.6.5 Sample size

We chose a sample size of 20 patients, 10 from each treatment modality. Based on the literature, we expect to reach a saturation of themes by this point ("the experience of *most* qualitative researchers (emphasis added) is that in interview studies little that is 'new' comes out of transcripts after you have interviewed 20 or so people" (Green and Thorogood, 2013, p.120)[336]). Previous experience within the department suggested that a saturation of themes usually occurred much earlier than 20 interviews (closer to 12). If new themes had still been emerging after 20 interviews, further patients would have been recruited until a saturation of themes was reached.

9.6.5.1 Data Collection

We conducted semi-structured interviews with patients in a place of their choice (subject to risk assessment). The interview schedule is included in Appendix.

Each interview lasted 30-60 minutes, or longer if the participant had further issues to discuss and was keen to proceed (a second interview was arranged if the patient so wished).

9.6.5.2 Data handling and record keeping

Names, hospital numbers, dates of birth and genders of patients, along with data relating to the outcomes of interest listed above, were collected from patients in accordance with the patient consent form, patient information sheet and the study protocol. We generated aliases for all patients which were stored with their real names and other data mentioned above in a password-protected database which was stored on an NHS machine.

Taking of consent and provision of information about the interview took place before recording started, to maintain anonymity. The interview was recorded as a WAV file using ClearRecord on a password-protected iPad in aeroplane mode (to prevent inadvertent copies uploading to the cloud). The files were transferred to a password-protected UCL machine via usb immediately following the interview, and were then deleted from the iPad. The files were labelled with the time and date of the recording, but no identifiable data was associated with the recording. Aliases were used for contemporaneous notes, and no names were used by the researcher during the recording. If patients did refer to themselves in a way which might be identifiable, this section of the recording was edited on return to UCL to remove the identifiable data prior to transcription.

The anonymised data was transcribed by an outside transcription service which is regularly used by Dr Low and has experience in transcribing sensitive interviews. The transcribed interviews were returned to Dr Alston for analysis using NVivo 10. Dr Alston also transcribed several of the interviews in parallel both to confirm accuracy of transcription and as a training exercise. University College London acted as the data controller for the study.

Dr Alston processed, stored and disposed of the patient information in accordance with all applicable legal and regulatory requirements, including the Data Protection Act 1998 and any amendments thereto. Patient data was stored centrally at the Centre for Nephrology as follows: the anonymised interview WAV files, the electronic copies of transcripts, and the NVivo database were stored in a password-protected folder on a UCL machine, and the database containing the aliases and real patient names was stored in a different password protected folder on an NHS machine. Consent forms, any hard copies of interviews or other paperwork were stored in a locked filing cabinet controlled by Dr Alston in the Centre for Nephrology offices (access requires both swipecard and keycode). There was nothing to link individual consent forms with hard copies of the interviews (they were filed separately).

The patient data was not transferred to any party except those identified in this protocol and was not processed and/or transferred other than in accordance with the patients' consent.

9.6.6 Data Analysis

Each interview was transcribed verbatim. The transcripts were transferred onto NVivo9, a software programme for analysis of qualitative data. The data was analysed using thematic content analysis. We identified key themes in the transcript and counted the frequency of these themes in the text. We undertook a thematic analysis of the transcripts to explore patients' understanding and experience of "distress" and factors contributing to it. Texts were re-read in their entirety to confirm key themes and place individual accounts in the context of information about each participant.

9.6.7 Withdrawal from study

If patients withdrew from the study at any point before or during the interview, or up until two weeks after the date of the interview, we removed all of their data from the study. After this stage the interview would have been transcribed and analysis would have started, and it would have been very difficult to remove the information at this stage.

9.6.8 Ethical Considerations

Ethics committee approval was obtained. Fully informed written consent was obtained from each participant in line with good clinical practice (GCP) as described above, including consent for audio recording. Data was treated confidentially as per the Data Protection Act (1998).

9.7 Results

9.7.1 Conduct of interviews

We recruited 19 participants, of which 7 were CKD4/5 and 12 were dialysis patients. 12 were men. There was a range of socio-economic classes, from professionals such as lawyers to retired barmaids. The mix of ethnic backgrounds was more limited, reflecting the area of north London from which these participants were recruited, but it included Jamaican, Irish, Jewish and mixed-race participants as well as white British.

There was a good rapport between interviewer and participant and I did not feel that my status as a healthcare professional prevented participants from speaking freely. Several did ask for medical advice, and needed to be redirected to their own medical team. Others asked me for clarification of medical decisions made by their team ("why might they have said that?"), and in those instances I asked the participant what they had understood at the time.

Although participants were very happy to talk, they were less able to introspect. Male respondents in particular had great difficulty in reflecting on the emotional impact that previous events had had on them. These respondents were from the generation of the "stiff upper lip", and are likely unaccustomed to interrogating their emotions. The female respondents, although of the same generation, were much more emotionally literate and could explain their thoughts and feelings much more readily.

9.7.2 What is distress?

The participants gave a wide range of definitions of distress. They described feelings of frustration and helplessness, concerns around change in self-image, grief, shock, empathy for others' suffering and physical discomfort. Constructing a coherent definition of distress is challenging; although each participant had a clear idea of what they meant by distress, individual definitions were often in

conflict. Definitions appeared to be informed by individuals' biographical narrative rather than being embedded in a shared social understanding.

Many participants described frustration and feelings of helplessness or powerlessness. For some this was provoked by physical limitations *("when you find that simple things, putting your socks on and things like that, you get very angry" – Michael, dialysis patient*). Other found their reliance on others frustrating (*"sometimes you know they'll be chatting and you think oh stop chatting and put me on"* – June, dialysis patient). Others described physical pain (*"No, the only distress that you get is if they take too much fluid off, where you get cramps"* – Wilbur, dialysis patient).

Miles, a retired accountant with CKD5, found his diagnosis of CKD distressing (*"Nobody likes to be told that they are not 100% healthy").* He described distress as a sense of disorder caused by the change in self-perception from "healthy" to "ill" *("Suddenly along the way you are suddenly told that there is something not quite right with you and you've got to eat certain foods or anything. That in itself is distressing. Because you are not the same person you were"*). He distinguished between severe distress which *"keeps you awake all night"*, and mild distress which he described as *"being upset"*.

Many participants experienced distress related to worries about their families, and Miles explicitly related this to his sense of helplessness when his wife was ill *("I can't help her. I could help myself by overcoming the distress myself, but I can't help her"*). Clive, a solicitor still working in his late 70s despite his CKD5, felt that distress was a more public phenomenon, which he experienced upon hearing about cases of child cruelty (*"Makes your blood run cold").*

Several described distress as "grief", and related their own bereavements as examples of distressing situations. In comparison, their own ill health was perceived as less distressing (perhaps because, as Miles explained above, their own health felt more within their control).

There was disagreement on how distress presents. One participant felt that distress *"comes out of the blue without apparent reason".* Another felt that distress *"can come and go"*. Yet another

described it as very transient: *"Little things. You get a bit under the weather for it, but not for the whole day. It's just a few minutes".*

Others felt that distress was a personal failing:

"I'm of the opinion that people these days have this huge feeling of entitlement, which is bloody rubbish. You've got to help yourself if you can" - Michael.

"*There's no way you can stop her being unhappy, she's not one of these people who will make an effort to be happy"* – Clive

Some participants did not associate their own negative emotional states with the term "distress":

"*I'm not distressed, the question that's missing off there is, frustration, huge"* - Michael

"I don't know if the word is distressed, worry I always say worry, I'm worried about this and I'm worried about that. Maybe I am distressed" - Jeanette

"*I think distressed is not a word I would use*" - Alan

This raises the possibility that the Distress Thermometer is not identifying participants who experience high levels of negative emotion but do not associate such emotions with their own definition of distress.

"*If this was a frustration thermometer? I'd be right at the top*" – Michael

The participants who did not identify with the word "distress" felt that distress was a very severe emotion ("*I think if you were distressed yes, you would be at your wits' end, you wouldn't know where to turn sort of thing"* – Jeanette).

Our explanations of the Distress Thermometer may need to reflect this to encourage patients to report milder symptoms, in order to allow HCPs to intervene before the symptoms become more troublesome. On the other hand, the original Distress Thermometer studies only intended the DT to detect "patients in significant distress" (Roth et al p1904)[278], so perhaps detection of milder distress

would simply lead to the pathologisation of self-limiting symptoms for which the patient has no need of our help.

There was recognition from some participants that distress was a broad concept:

"I mean I know distress can mean pain, it can mean all sorts of different things, but yeah that's what that would mean to me" – George.

"*You've got something wrong with you you're distressed about it. You can also be distressed about other people's conditions, you can be distressed about world conditions!"* –Clive

9.7.3 **Depression v Distress**

There was a fairly even split between those who felt that distress was the same thing as depression, and those who felt it was not. Interestingly, those who felt it was different to depression were divided on whether distress was more or less severe than depression – Samuel described distress as *"a calamity",* whereas Jasmine said that *"to me, distress is when something is not right and it's bugging you. Depression is when you see no way of surviving".*

Miles differentiated between depression which "*can come upon a person out of the blue without apparent reason*" and distress where "*something has caused it, yes. I don't think you get distressed for no reason. You get distressed because something has actually caused it*". This echoes the concept of "secondary depression" affecting dialysis patients, described by Mimi Israel[337]. There is extensive debate within the psychiatric community about the differences and demarcations between depression as a psychiatric illness and normal grief response to traumatic or upsetting events (reflected in the controversy over the removal of the Bereavement Exemption in the DSM-V[338,339]), and it is interesting that, colloquially, participants seemed to understand this distinction.

9.7.4 **Causes of distress in CKD4/5 patients**

As we had hypothesised, the causes of distress were different for participants who had CKD4/5 and those who had already started dialysis.

For those participants with CKD4/5, there was a division between those who felt distressed by their diagnosis of CKD, and those who tried not to think about it. Those who felt distressed by their diagnosis reported a change in self-perception as a result of the diagnosis:

"*I never ever went to the doctor until I was at least 70 and I was always very fit*" – Michael

"*No. I don't think of myself as a patient particularly*" – Clive

"*All my life I have been fairly healthy. Suddenly along the way you are suddenly told that there is something not quite right with you and you've got to eat certain foods or anything. That in itself is distressing…because you are not the same person you were. That is distressing*" – Miles

"*This one kind of floored me because I just got it into my head that I was going to die and that's it*" – Mary

Some mentioned the sense of unfairness they felt on diagnosis despite being a "*good patient*" (Alan) by following medical advice. Hazel specifically mentioned the outrage she felt when other patients "cheated" ("*I thought, that's not on your diet!*"). Diets in general were felt to have an almost talismanic ability to protect against dialysis ("*I kept a diet and everything so I should be okay*" – Miles; "*I asked what I could do for myself and the answer was nothing really. I said I'm not having that so I did change a few things in my life*" – Hazel). This may be because diet is seen as an area within patients' own control.

Others reported that they had initially been disturbed by their diagnosis, but as time had passed and nothing had happened, they had been reassured by the fact they were not receiving active treatment:

"After a few months when it was found that it was more or less like stale mate, it hadn't got worse thank god, so they stopped worrying" – Miles

"The fact that I had no symptoms, and if I hadn't been told, wouldn't have known and didn't think it was getting any worse until as I say I was told I'd progressed from 3 to 4, I won't say it lulls you into a sense of false security but it prevents you being alarmed doesn't it" – George

"I said to him in some alarm [laughs] oh what do I do about it? And he said nothing!" - Clive

The participants with CKD4/5 all found the idea of dialysis distressing. Some compared dialysis with death ("*it's more or less a death sentence isn't it. I called it a death sentence but I suppose a life sentence is more accurate*" – Clive). Others simply refused to discuss it or consider it at all, preferring to put off any decisions till the future. The implication was that, by putting off dialysis decisions, they may also put off dialysis itself.

It was widely assumed that healthcare professionals were motivated to initiate dialysis, and there were several comments about not "letting" doctors start them on dialysis, and "playing along" with doctors in order to avoid further discussion: *"I took the leaflets and I read them and I thought no way am I doing this. But he said we have got to have a plan what you want. So I agreed I would probably look at home dialysis if it was appropriate and left it at that. No way."* - Hazel.

9.7.5 **Causes of distress in haemodialysis patients**

Some of the dialysis patients reported that they had been "pushed" into dialysis unwillingly, rather than it being a treatment decision that they had made themselves. However nobody wished to withdraw from dialysis. The ambivalence appears to represent sadness about the necessity of starting dialysis, rather than regret that they had not chosen the Supportive Care pathway instead.

Many participants described an intense period of distress around the time of start of dialysis. Beatrice described dialysis "*it's terrible. I'm losing all my life because I'm either here or I'm asleep*".

Aidan commented "*Well, I was told that it wouldn't be a pleasant experience, and it hasn't been pleasant*".

Mary "*cried for two weeks. When they told me I got to have dialysis I was devastated, devastated".*

None felt any better since starting dialysis. On the contrary, Aidan felt that he "*seemed to deteriorate*", and Alan complained of "*Pains. Energy. Tiredness. Ability to run up and down stairs. It's all different. My life is very different now*".

9.7.6 **Association between dialysis and death**

As well as the idea mentioned previously that dialysis was "a death sentence", some participants associated dialysis with death in a more literal sense.

Jeanette described observing other inpatients who were already on dialysis, and wondering whether the same fate awaited her: "*She'd come back upstairs, they'd leave her in bed and she seemed to sleep for a while and I would watch her to see if she was all right because I thought I wonder if she's going to die. That was my thought, everybody's going to die, me too."*

Samuel also reported a frightening discussion he had with a neighbour who was already on dialysis (who was unaware that Samuel had CKD too): "*Well I will tell you. My neighbour upstairs right at the stairs, he was on dialysis and he recently died about a year ago. Yeah. He was a bit older than me. I met him one day out in the car. He said to me… he didn't know anything about me. He said to me it's a death sentence. That is what frightened me. I don't feel I want to die*". He went on to explain that another acquaintance on dialysis had also died: "*So all the people you have known with kidney disease, it has not been very positive?"* "*Well yeah, yes. It's only two we've known. They both died*."

Interestingly, Albert described several extremely traumatic events – witnessing the deaths of two of his cohort in the bay in front of him during dialysis sessions, and the experience of his own cardiac arrest on dialysis – but denied feeling any distress about these events, and seemed puzzled at the

suggestion that he might have found them upsetting. His method of dealing with things was not to think about them "*Well … you know, I just feel a bit … it could happen to me … but, you know [laughs], what can you do about it? You could be walking along – you could be getting on the bus, and drop down dead. So … that's it*".

And although Jasmine claimed to have "*taken it all in stride*", she still remembered the exact date of her first dialysis session fifteen years ago, suggesting that she saw that date as a significant one.

9.7.7 **Intrusiveness of dialysis treatment**

The main reason that participants with CKD4/5 wished to avoid starting dialysis, and the main complaint from those participants who were already on dialysis, was the intrusion into and impact on the rest of their day to day lives ("*it interferes with your life to such an extent that whether or not you're doing much [laughs] you you you you shrink, you shrink very much in thought*" – Clive).

On this background, delays (such as delays due to problems with patient transport, or delays being put onto machines) were a major source of distress. Participants reported that these delays increased their sense of constraint and lack of control. There was a strong feeling that delays were avoidable and due to inefficiencies in the service – participants did not blame the individual staff for this (they generally praised the dialysis nurses and individual drivers for being hardworking, although this may have been partly because they were aware that I am a HCP, or because they did not want criticism to get back to the staff). Instead they blamed underfunding of the service, and incompetence of the transport managers.

Participants reported that being on dialysis was bad enough, and that delays made this worse than it needed to be. Delays were interpreted as a lack of concern for them as patients, a lack of courtesy and respect, and left participants feeling disempowered and "like a cog in a machine" rather than being treated as an individual.

Patients who organised their own transport felt more empowered and happier than those on hospital transport. However, they were distressed by delays waiting for machines to be ready, because this made them keep other people (their taxi drivers) waiting.

June expressed distress that her carers arrived at unpredictable times, and this meant that she often was not ready for the transport driver. To manage this, she had started getting up at 4am on dialysis days in order to get herself ready on her own ("*I can't bear unpunctuality, I'm always fifteen minutes early, been like that all my life*"). She would rather inconvenience herself than keep others waiting, as this allowed her to retain some control of the situation ("*you know, to have to rely on other people for things, eh it does get a bit annoying*").

9.7.8 **Managing distress**

Following the initial grief/trauma response that many participants reported upon starting dialysis, most participants described a process of adaptation to dialysis ("*I wasn't very happy to start with. Of course I've gotten so used to it now"* – June). This was not always done willingly! ("*I adjusted to my illness. Because it can't adjust to me. I made up my mind on that bit, that I have to adjust to my illness*" - Hester).

Jasmine explained how one of the ward nurses had helped her to adjust: "*You know you read a book and starting reading, it's so interesting. Then you suddenly come to a page and you can't come off that page because the whole thing is gone, funny enough. You read that line and you leave it and you come back and you read the line but you're not reading it like how you were reading it before. And I said to her 'After you left I was thinking about it. So when I got up in the morning I felt much better.' So I said to her 'I have turned the page and moved on'*."

Other methods used to manage distressing situations included practicing acceptance, and having a sense of fatalism ("*I wish I didn't have to, but I know I have to. So there is no fight, you know"* –

Hester; "*Having to take enforced retirement through health wasn't something I either had planned for or wanted. But it happened. I had no choice*" - Alan).

In particular, participants accepted that ill health was a normal part of ageing ("*Well I'm elderly. People's health does deteriorate as they get older*" – George; "*You're getting old, things are bound to stop working*" – Michael). Some accepted death as part of this ("*all these ailments – you know, so I'm … I'm quite reconciled to the end, when it does come*" – Aidan). Others felt quite the opposite, and fought against their mortality ("*I said you've got the wrong person, I don't behave like that [Laughs] To me life is very precious. And having got it I intend to hang on to it as long as I can*" – Alan).

Some participants compared themselves to other patients around them, and felt that instead of being distressed about their own situation they should be grateful for what they had ("*I think yes, some of them are probably worse than me so I shouldn't be feeling sorry for myself*" – Jasmine).

Several participants had made a conscious decision to be positive about their situation – these participants could point to a specific moment when they decided to accept things ("*Then I decided just to bear it, I'm not letting it get the better of me, I'm just not, I'm going to get up and do what I've got to do, even going for this*" – Jeanette; "*So you know a lot of thought went into it and what I do is I adjust. I adjusted myself because I realize… I didn't fool myself. I adjusted myself and didn't fool myself and come to the expectations that my life would become any different*" – Hester).

Many mentioned their "placid" personality as a protection against distress. They also mentioned their relationship with other patients, and the sense that the dialysis staff cared for them and treated them with respect.

Dialysis was not discussed between the other patients; instead they distracted each other from their situation ("*We didn't really talk about the dialysis, we talked about everything else. It's funny, sometimes, you want to hear the laughter that comes out of here at times, it really cheers you up*" – Beatrice). Other patients who broke the social contract of positivity were viewed with disdain ("*This woman said to me one day 'I can't see why you're laughing. This is nothing to laugh about.' So I said*

to her 'Look, if you cry you cry alone but if you laugh the world laughs with you.' She said 'Well I'm not laughing because it's not funny'." – Jasmine).

9.7.9 **Maintaining sense of self**

Participants did not wish to be defined by their renal disease. Instead they made great efforts to maintain their previous sense of self despite the limitations imposed by their illness. There were differences between the genders: men often talked about past career successes ("*I ended up with over a million visitors in a year. I think we made thirty thousand quid in turnover in our first year or something*" – Alan). Others explicitly defined themselves by their previous career ("*Looking at me you see the result of being a lawyer for all that time*" – Clive).

Geoff used his previous experience in management to analyse the problems in the dialysis unit ("*There is no doubt that the staffing is not adequate, and I've spent a lifetime career looking at staffing levels. There's a formula that you have to apply to any staffing levels. You add 13 percent on for sickness and holidays*"). By asserting his authority as a professional, Geoff rejected his status as a patient. He had also befriended his GP and went on holidays with him, again subverting the doctor/patient power dynamic.

In contrast, the women talked about their families. They explained long-running family feuds, proudly told of their children's successes, and positioned themselves within a framework of interlocking relationships. They were keen to protect their families from anxiety ("*Yeah, I couldn't talk [to my children] about it in the beginning*" – Jasmine), but also described the feeling of security they derived when their families took over caring commitments ("*She did everything, she looked after me like nobody's business*" – Mary).

Participants also made strenuous efforts to maintain their physical independence – as previously mentioned, many organised their own transport to and from the dialysis unit. Others sadly described

the limitations on their freedom now that their mobility was impaired ("*All these things that you took for granted that you could do, you now find that they are difficult*" – Michael; "*I used to go out and do my shopping. I used to take a taxi and go to places. You know, you just did normal things. But I can't do it so much now*" – June). Beatrice described the indignity of needing her son in law to help with her personal care ("*It is embarrassing and upsetting, very upsetting actually. But what can you do, it's got to be done, there's nothing you can do about it*").

9.7.10 Information about dialysis

Participants with CKD4/5 were generally quite reluctant to receive information about dialysis, or to make future plans ("*I'm the type of person, I don't like to ask questions, I think ignorance is bliss*" – Jeanette). They wished to maintain the status quo, and seemed to view dialysis as an event far in the future which might never happen *("I'm just hoping I won't need it… 90% of the time the thing that worries you doesn't happen, it doesn't come to fruition*" – Miles). Receiving information about it ahead of time was seen as pointless, as Hester stated "*Wait until that time comes. I don't know what is going to happen in two years' time. That is too far ahead for me*".

Clive was unwilling to make any kind of preparations for dialysis at all ("*I'm very much a bury-your-head-in-the-sand man, I am*"). Miles did not feel that he could make a decision on whether he would want dialysis or not until he was "*at that point [of needing dialysis]".* He felt that this dislike of change was part of getting old: "*It's only when you are old and you get set in your ways that you can't get used to things. I wouldn't like to change now, I wouldn't like any sort of change now. I wouldn't like any sort of change*".

Many CKD4/5 patients were reassured by fact that no "active" treatment was require for CKD ("*Because it has got no physical alteration in my life, no, I don't think about it*" – Miles). Several

participants explained that the doctors were "just monitoring" them, so they did not think that their kidney disease was all that serious.

Those on dialysis did not want to consider withdrawal from HD or to imagine health worsening, even when they reported that their health was much worse than it had been prior to starting dialysis. They had unrealistic expectations of life expectancy on dialysis ("*I've reached 74 and a bit, I don't want to go yet. If I get to eighty something I think no, no. I don't want more fiddling about*" – Hazel). There was no sense of planning for end of life, even though some patients were clearly aware that their life expectancy was limited ("*I expect that I won't live much longer – you know, with all these … cos of … a, a dicey heart*" – Aidan).

We discussed whether participants would like to meet (or if they were on dialysis, would they have liked to have met) other people who had been in their position to learn about their experience of starting dialysis – nobody thought that that would be helpful ("*Something like that you are far better off finding out for yourself. Because the way it affects one person doesn't necessarily affect another one the same*" – Beatrice; "*I don't think so, because it was the experience that one would have to go through oneself*" – Aidan; "*No, I don't think so. I mean, I've got the leaflets, I can read those" -* George).

Indeed, Hazel felt it would have been actively unhelpful: *"I don't think it would have done me much good to talk to people about it. They might have said the wrong thing and if they had been upset with it I really wouldn't want to know that*".

9.7.11 **Living with uncertainty**

Attitudes towards the uncertainty of living with CKD were split – as previously discussed, some clung to the fact that "*it [dialysis] might never happen*", while others found the uncertainty to be a source of distress.

George explained that "*In a way it was good news in that it is not immediately. But in other senses it is not good news because it is sort of deferring it. It's the sword of Damocles*". In particular, he was disconcerted that the lack of symptoms gave him no indication of whether his CKD was better or worse "*because you got no idea where you are. At least with the arthritis you know where it is because you can feel it all the time*".

Interestingly, several participants who had started dialysis reported that it was not actually as bad as they had feared ("*Frightened of the unknown, I was scared*" – Jeanette; "*I was all a bit scared but now I'm used to it I don't even think about it really. It's like everything once you get used to it*" – Beatrice).

9.8 Discussion

9.8.1 The Meaning of Distress

When asked to define distress, participants provided a wide variety of responses, which while thematically interconnected, are nevertheless broad enough to include critical ambiguity and contradiction. What, for example, is the experience of distress? For some participants, it was self-described as a negative emotional state (as per the NCCN definition[277]), for others a rational concern, and for others again a bodily discomfort.

Similarly, where the locus of distress? For some, distress emerged from within the self, in particular around negative changes in self-image or sense of control. For others it came from without, generated by reflecting on the suffering of others, be they immediate family members or victims of war on the news. Most commonly, distress is understood to reside in an interdependency of self and world, described as a response to negative events in that participant's life and characterised as frustration, anxiety, worry, and so on.

Such is this interdependency that participants often struggled to distinguish the experience of distress from the causes of distress, describing a distressing situation when asked to describe distress itself. The concept of distress, then, is caught in a tautological circularity – distressing events are distressing because they cause distress, but equally distress as an experience is defined as the state which is caused by distressing events. Is this circularity problematic? Not if we posit that distress as a phenomenon is intrinsically socio-spatial, as it appears to be, being tied into patients' immediate experience of the world, their conceptual models of the world, their cultural background, their personal biography, and their sense of place in society.

Given the range of opinions on offer, can we pin down a single definition of distress that covers all participants' definitions? To do so means mobilising a suitably wide definition so as not to exclude any of the perspectives discussed. Hence the utility of the proposal that distress is the “negative emotional experience of the individual” (National Comprehensive Cancer Network[277]) which effectively encompasses the variety of participant viewpoints, being broad by design.

That said, while we as researchers we can come to some consensus around a technical definition, amongst the population as a whole, in the breadth and fluidity of possible definitions, distress as a term should be understood as a floating signifier[340]. That is to say, in use, the word “distress” does not unambiguously refer to any one concept, experience, or phenomenon, but rather is a cluster of related terms, with meaning generated idiosyncratically by each individual. To understand any individual's notion of distress, one must interrogate how the term is shaped by the lens of their history, attitude to life, memories, associations, and values.

The question is, then, what impact this definitional fluidity has on the Distress Thermometer as a diagnostic device. Firstly we must acknowledge that asking patients to define distress is somewhat of an artificial exercise – in practice, the Distress Thermometer is designed to work with whatever definition of distress each patient deploys, without challenging them on that definition. Secondly, we

should note that while definitions of distress may vary across a population, for any individual, distress is a stable, common sense term that presents little difficulty in comprehension.

In fact, far from problematic, it is the nature of the distress as a term that makes it so useful for this task. In being productively ambiguous, it is capable of embodying multiplicitous nuance, and so can map onto each individual's own personal understanding of distress. While patients may disagree amongst themselves as to what distress truly is, for each individual, distress provides a single intuitive metric that is quantifiable, can track change over time, and easily facilitates conversation with practitioners.

If there is a concern to be had with regards to how patients define distress, it is around those participants who distanced themselves from the notion of distress itself. Although we might still say that these patients experience some degree of distress, they would not agree, perhaps because they associate distress with a degree of severity that they don't feel they experience, or because it is related to an inability to cope when they feel like they are coping well. For these patients, it would be useful to provide an alternative definition that allowed them to express their distress without appeal to the word itself.

9.8.2 **Clinical implications**

9.8.2.1 Distress around initiation of dialysis

Distress appeared in this study to be a near-universal response to the transition onto dialysis. Both the threat of impending dialysis and the upheaval caused by the initiation of dialysis were described as distressing. However, the majority of participants who had been on dialysis for some time reported an acceptance, or resignation, to their new circumstances, with an according reduction in their distress levels.

It is important to avoid pathologising a normal transition onto dialysis. The impact of haemodialysis on a patient's life is immense, and it is understandable that many experience a sense of loss for their old life, approaching a grief reaction. Parker et al found that "serious medical problems" (which must surely encompass initiation of dialysis) were equivalent to bereavement in terms of psychological impact[341]. It may not be possible, or even desirable, to prevent patients from being upset by this unlooked-for change.

However, the Hedonic Treadmill Model[342] would suggest that the majority of patients return to their baseline level of happiness given time to adapt psychologically (this level of baseline happiness would of course vary from individual to individual[343]). This study appears to support that supposition. So should we intervene only on those patients in whom the adaptive process is maladaptive, prolonged or severe? These patients would likely meet the criteria for Prolonged Grief Disorder, now included in the DSM V[344], and thus may benefit from medication or renal psychology input. The Distress Thermometer may be used to detect these patients, or alternatively renal services could ensure close attention from the named dialysis nurse for the first few months on dialysis, and rapid referral if there are concerns about adjustment.

9.8.2.2 Reducing distress

In terms of mitigating the wider causes of distress, Morse[345] discusses the common responses and coping mechanisms to threats to sense of self, and this framework provides a useful framework for interpreting many of the themes reported by our participants.

She describes the "salvaged self", or maintenance of a previous identity despite a current inability to function in that role. We saw this in the way participants used their previous careers as a lens through which to interact with the dialysis unit. We also saw the disproportionate impact that delays had on a participant's distress levels. Interestingly, this was not due to the intrusion of the delays

themselves into the rest of the patient's life (most participants went straight home after dialysis anyway), but was due to the perception that these delays created that the participant was seen as "a cog" rather than an individual.

Small initiatives from staff to recognise patients' individuality and existing skills (for example patient consultation groups) are likely to have a disproportional impact on patient satisfaction. Substantially more effort is needed to avoid delays in transport and in having machines ready for patients – this could include split dialysis shifts, or an increase in dialysis self-care (so they can put themselves onto dialysis when they arrive without needing to wait for a nurse to become free).

The desire to maintain the status quo has been previously described by Llewellyn et al[346] in patients with CKD4/5 who elected not to have dialysis. We found a similar picture in our study. This wish to maintain the status quo included a wish to avoid hearing about dialysis and to "stick your head in the sand" instead. Giving information at a time when patient does not wish to receive it is likely to be counterproductive – the patient will find this distressing and the information is unlikely to be retained. Of course the clinical situation may supersede the patient's wish to defer discussions!

However the use of a Buddy or peer-support system may be better accepted if it is offered once on dialysis (ie as a "dialysis mentor" scheme for new starters, rather than as part of the pre-dialysis education programme).

9.8.3 **Limitations and Unanswered Questions**

The major limitation to this study is the small number of black and minority ethnic participants recruited. Several BAME patients were approached, but many older South Asian participants were non-fluent in English, and others declined to take part. Religious and cultural beliefs may also play a role in the attitudes of some patients to distress and suffering.

The association between dialysis and death suggests a potential link between the distress experienced around dialysis initiation and the phenomenon of grief. It would be interesting to explore how far participants agree with this position, and whether interventions for prolonged grief reactions or trauma are helpful in easing the transition onto dialysis.

Some of the participants were quite unable to reflect on prior distressing events in their lives, which may be a protective response ("burying one's head in the sand") or may be due to an upbringing in which emotions were not discussed or displayed. This resulted in the situation where Albert insisted to me that his own cardiac arrest had not distressed him as he never thought about it.

We also spoke little about dialysis withdrawal, and I suspect that the wish to maintain the status quo and to avoid engaging with upsetting future events (which emerged strongly from my interviews, and which was also described by Llewellyn et al[346]), would play a large part in influencing attitudes towards palliation and cessation of dialysis.

10 Conclusion

10.1 Use of mixed methods in this project

From the initial planning stage of this thesis, it was clear that my research question mandated a mixed method approach. Questions such as "what do patients mean when they say they are distressed?" could not be answered using a quantitative approach, and "what are the risk factors associated with increased DT scores?" is clearly best answered with a quantitative approach.

The gaps in the existing distress literature, such as lack of clarity about the definition of distress within individual papers, and lack of consensus between researchers, suggested that my thesis would benefit from a multi-paradigm approach. This approach provided two benefits[301]: both complementarity (allowing me to explore different aspects of the phenomenon of distress), and triangulation (providing confirmation of my findings from multiple sources, for example both the Cross-sectional and Trajectory studies found similar risk factors for high DT scores, despite using data from different cohorts).

I initially conceived of this thesis as a quantitative-focused mixed methods study. However as my work developed, I discovered that the insights into distress which I gained from the qualitative work was the key to understanding the experience of distress. The quantitative studies left me with many questions – who do some people with high depression scores say that they are not distressed? Why do some participants' DT scores go up when they start dialysis, when others do not? The qualitative study allowed me to understand my quantitative data better, and made sense of the sometimes confusing results.

The use of mixed methods sits well within the paradigm of interpretative phenomenology. In my interviews I examined the phenomenon of distress through the lens of multiple different patients. In the wider thesis, I examined it through the lens of both qualitative and quantitative paradigms, and

from the "snapshot" perspective of the cross-sectional study and the longitudinal perspective of the trajectory study. In this way I was able to construct a theory of distress from many different angles.

This is fitting; I found that distress itself extends across the physical, discursive and clinical domains, so it is unsurprising that multiple approaches were needed to give a complete picture. I have synthesised the results of the four studies into the six overall research questions below.

10.2 Summary of Key Findings

10.2.1 Is the DT an acceptable tool for use in CKD4/5 and dialysis populations, and what is it measuring?

It appears to be both quick and acceptable, taking 3-5mins to complete. We found a close relationship between the DT and both the HADS and BDI-II, in terms of both a general correlation between scores, and between higher DT scores and 'caseness' on the HADS and BDI-II (AUC 0.87 and 0.76 respectively).

The relationship between HADS and DT scores did vary over time, for unknown reasons. This variation appears to be related to the participant. In contrast, the relationship between BDI-II scores and distress was stable over time, but little of the variation in the relationship (22.2%) was due to differences between participants.

There was a correlation between increasing MSAS total scores (ie increasing symptom number and/or severity) and distress, and an inverse correlation between all subscales of the SF-36, suggesting that distress worsens with worsening quality of life. The strongest correlations were between DT score and the Energy and Emotional Wellbeing subscales.

The DT has been validated in many different diseases, but to our knowledge this is the first time it has been used in renal patients.

10.2.2 **Is Distress the same as Depression?**

Findings from both the validation study and the interview study support the conclusion that, while distress is closely associated with depression, it is not the same thing.

Despite the good agreement between DT scores and "caseness" on the HADS and BDI-II, there were plenty of participants who scores highly on the DT but did not meet the criteria for depression on the other tools, and those who appeared meet the criteria for "caseness" on the HADS or DT but who did not report high levels of distress.

Participants in the interview study differentiated between distress (which could come and go, and had an identifiable cause) and depression (which was there constantly and for no reason). Opinions on the relative severity of depression and distress varied, but a distinction was made between the two things in most cases.

The originator of the DT, Roth[278], did not intend distress to be thought of as the same thing as clinical depression. Neither do the DT copyright holders, the NCCN[277], who use the term "negative emotional experience of the individual". The whole advantage of the DT is its flexibility and ability to encompass a wide range of negative emotions. It is productively ambiguous. While patients (and staff) may disagree amongst themselves as to what distress truly is, for each individual, distress provides a single intuitive metric that is quantifiable, can track change over time, and easily facilitates conversation with practitioners.

10.2.3 **How can we define Distress?**

As mentioned above, the NCCN defines distress as "the negative emotional experience of the individual". This broad term is difficult to improve on, given the broad range of emotions and experiences described by our participants.

Participants in the interview study often struggled to distinguish the experience of distress from the causes of distress, describing a distressing situation when asked to describe distress itself. Distress behaves as a "floating signifier"[340]; to understand any individual's notion of distress, one must interrogate how the term is shaped by the lens of their history, attitude to life, memories, associations, and values.

10.2.4 **Which patients are more likely to be distressed?**

The cross-sectional study found that younger patients, female patients, those with a pre-existing diagnosis of depression, and those on haemodialysis had significantly higher rates of distress.

Previous studies have reported that younger patients are generally more distressed than older patients[284,323,324], and the fact that those with a pre-existing diagnosis of depression were more likely to be distressed should come as no surprise. However, to my knowledge no previous studies have made an association between distress and gender (many studies on distress have been carried out in cancers which generally affect one gender only, such as prostate cancer). The finding that haemodialysis patients are significantly more distressed than patients with CKD4/5 is also novel, and complements existing work showing high levels of depression[156] and poorer quality of life in HD patients[17].

The longitudinal study also demonstrated high levels of distress in patients with poor functional status – this may be due to sadness at not being able to do the things that they enjoy, frustration at being dependent on others, or even due to physical pain or high symptoms burden from underlying medical problems. Again, this is a novel finding.

10.2.5 How does distress change around the start of dialysis?

The DT trajectory study found that, for the majority of participants, there is a rise in DT scores around the time of initiation of dialysis. For some of these participants, distress levels returned to baseline after a couple of months. However for a substantial minority, distress levels remained elevated up to one year post-initiation of dialysis.

In the interview study, Distress appeared to be a near-universal response to the transition onto dialysis. However, participants who had been on dialysis for some time reported an acceptance, or resignation, to their new circumstances, with an according reduction in their distress levels. Although they did not enjoy dialysis, it no longer caused them distress. The concept of psychological adaptation, described in chapter 10, is likely to be in effect here.

I am not aware of any other published studies assessing change in distress over time before and after a traumatic event (for cancer patients, it would be difficult to recruit participants prior to their diagnosis). Da Silva Gane et al[17] assessed change in self-reported quality of life before and after starting dialysis and found that quality of life did decline in haemodialysis patients, but there was no evidence of return to baseline in this study.

10.2.6 What are the causes of distress and what can be done to mitigate this?

In the interview study, both the threat of impending dialysis and the upheaval caused by the initiation of dialysis were described as distressing. This was attributed by patients to a fear of the unknown, a desire to avoid change and disruption, and concerns about the impact that dialysis would have on the rest of their lives.

Other sources of distress were functional decline and increased reliance on others, family problems, and wider societal problems.

Techniques that participants used to mitigate distress included denial, avoiding information about dialysis, and putting off decisions until the future. There was a sense that life was short and unpredictable, and that there was no point in worrying yourself about something that was in the future.

In terms of HCP interventions, the main point of contention for patients was the delays associated with dialysis and hospital transport. Some patients had addressed these problems themselves by organising private taxis, but efforts from the healthcare team should also be made to improve this.

10.3 Implications for practice

How does this affect how we use the Distress Thermometer? In the first instance, we should recognise that the Distress Thermometer is a discussion aid, rather than a diagnostic tool. Participants who score highly on the Distress Thermometer may be depressed, but they may also have high symptom burden, be worried about their daughter, or be anxious about starting dialysis. The only way to truly understand the significance of a high DT score is to discuss that score with the patient themselves, in order to contextualise the score within their wider experience.

We should take high scores seriously – DT scores greater than 5 have a specificity of 75% for depression on the HADS or BDI-II. We should be particularly vigilant for signs of distress in younger patients, women, and those with existing mental health problems.

We should also target our dialysis education slightly differently – currently we reassure patients that "they might never need dialysis", which they interpret as meaning that they can put it out of their mind. However many of our participants found the uncertainty difficult to cope with, echoing the finding of Gilbar et al[296] that denial as a coping mechanism was, contrary to expectation, not associated with lower distress. From a clinical perspective, dialysis modality decisions are best made

in the calm environment of an outpatient clinic, rather than as an emergency in A&E in the middle of the night. Some decisions cannot be put off till the future.

A change in focus from peer educators in Low Clearance Clinic to "Dialysis Buddies" after initiation of dialysis may encourage greater uptake of this resource among older patients. Certainly new starters on haemodialysis are at a vulnerable stage, and need close monitoring to ensure that they are adapting to their changed circumstances. There is no need to pathologise the normal process of adaptation, but a significant minority will not adapt after six months on dialysis, and those patients may benefit from increased psychological support.

10.4 Implications for future research

Researchers who wish to use the DT as a marker of overall negative emotional experience need to be aware of its limitations. In particular, as distress is self-defined, there will be a subset of participants who do not share the researchers' concept of distress which may lead to information bias (as the DT may not be measuring what the researchers think it is measuring).

Furthermore, the fluctuating nature of distress (see Figure 6.28) means that any longitudinal studies which use the DT will need to be appropriately powered to avoid spurious results due to background variability. In particular, in light of the multiple trajectories of distress which we identified around the time of dialysis initiation, any future studies which use the DT to monitor response to an intervention (such as referral to psychology) will need to avoid misclassifying the improvement in distress that many patients achieve without intervention (as part of normal psychological adjustment), as an effect of the intervention. A good control group will be key here.

The next logical step is a larger scale longitudinal study, following participants for a year before and after starting dialysis but with a large enough cohort to investigate the factors affecting trajectory of distress using quantitative methods.

It would also be extremely interesting to investigate the relationship between distress and frailty. As there is an association between DT score and functional status (as measured by the KPS) there is a good chance that frailty will indeed be associated with DT scores. Frailty is extremely common in dialysis patients (much more common than in the general population), and the frailty phenotype is defined as worsening functional status and strength, weight loss and exhaustion.

Appendices

11 Appendix A: Research Ethic Committee Approval Letters

NHS
Health Research Authority
NRES Committee North East - Newcastle & North Tyneside 2
Room 002
TEDCO Business Centre
Rolling Mill Road
Jarrow
NE32 4BW

Tel: 0191 428 3565
Fax: 0191 428 3432

4 April 2013

Dr Helen Alston
Centre for Nephrology at UCL
Royal Free Hospitals NHS Foundation Trust
Pond Street
London
NW3 2QG

Dear Dr Alston

Study title:	**Validation of distress thermometer in a UK renal population**
REC reference:	**13/NE/0087**
IRAS project ID:	**115488**

This application was originally reviewed by County Durham & Tees Valley REC which is now closed as of 31.3.13

Thank you for your notification of 3 April 2013, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Gillian Mayer, nrescommittee.northeast-newcastleandnorthtyneside2@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

NHS
Health Research Authority
NRES Committee North East - Newcastle & North Tyneside 2
Room 002
TEDCO Business Centre
Rolling Mill Road
Jarrow
NE32 4BW

Tel: 0191 428 3565

14 June 2013

Dr Aine Burns
Consultant Nephrologist & Honorary Senior Lecturer
Royal Free Hospitals NHS Foundation Trust
Pond Street
London
NW3 2QG

Dear Dr Burns

Study title:	**Validation of distress thermometer in a UK renal population**
REC reference:	**13/NE/0087**
Amendment number:	**Amendment 1 (10/5/13)**
Amendment date:	**14 May 2013**
IRAS project ID:	**115488**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Information Sheet: Patient Information Sheet - Validation of the Distress Thermometer in a UK Renal Population	1.2	10 May 2013
Protocol	1.3	10 May 2013
Notice of Substantial Amendment (non-CTIMPs)	Amendment 1 (10/5/13)	14 May 2013

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Business Services Organisation

Office for Research Ethics Committees Northern Ireland (ORECNI)

Customer Care & Performance Directorate
Office Suite 3
Lisburn Square House
Haslem's Lane
Lisburn
Co. Antrim BT28 1FW
Tel: +44 (0) 28 9260 3707
Fax: +44 (0) 28 9260 3819
www.orecni.hscni.net

HSC REC 2

22 May 2013

Dr Aine Burns
Consultant Nephrologist and Honorary Senior Lecturer
Royal Free Hospital NHS Trust
Royal Free Hospital
Pond Street
London
NW3 2QG

Dear Dr Burns

Study title:	**Longitudinal models of distress in older renal patients research study**
REC reference:	**13/NI/0075**
IRAS project ID:	**85168**

The Proportionate Review Sub-committee of the HSC REC 2 reviewed the above application on 22 May 2013.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details. Unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Mrs Katrina Greer, katrina.greer@hscni.net

Ethical opinion

On behalf of the Committee, the sub-committee gave a **favourable ethical opinion** of the above research on the basis described in the application form, protocol and supporting documentation, **subject to the conditions specified below**.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 5
Ground Floor - Tennent Building
Western Infirmary
38 Church Street
Glasgow
G11 6NT

Date 14 May 2014

Direct line 0141 211 2102
E-mail WoSREC5@ggc.scot.nhs.uk

Dr Aine Burns
Consultant Nephrologist
Royal Free Hospital NHS Trust
Pond Street
London
NW3 2QG

Dear Dr Burns

Study title:	**Distress in Older Renal Patients Interview Study**
REC reference:	**14/WS/0120**
Protocol number:	**14/0267**
IRAS project ID:	**130178**

Thank you for Ms Alston's email of 14 May 2014, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the lead reviewer.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Mrs Sharon Macgregor, WoSREC5@ggc.scot.nhs.uk.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

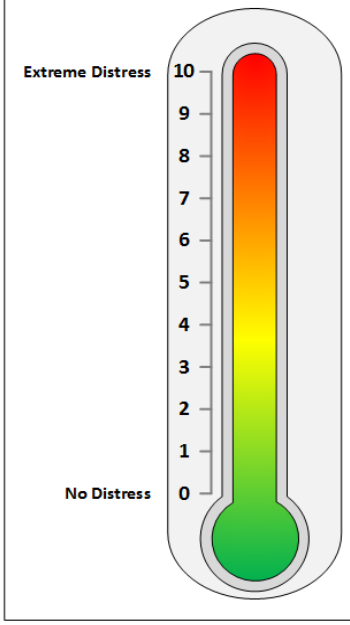
The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

12 Appendix B: Reference Tools and Questionnaires

The Distress Thermometer

1. Please circle the number (0-10) that best describes how much distress you have been experiencing in the past week including today.



2. Please indicate if any of the following has been a problem for you in the past week including today. Be sure to check YES or NO for each.

YES	NO	Practical Problems
☐	☐	Child care
☐	☐	Housing
☐	☐	Insurance / financial
☐	☐	Transportation
☐	☐	Work / school

YES	NO	Family problems
☐	☐	Dealing with children
☐	☐	Dealing with partner
☐	☐	Dealing with close friend / relative

YES	NO	Emotional problems
☐	☐	Depression
☐	☐	Fears
☐	☐	Nervousness
☐	☐	Sadness
☐	☐	Worry
☐	☐	Loss of interest in usual activities

YES	NO	Spiritual / religious concerns
☐	☐	Any spiritual / religious concerns

YES	NO	Physical problems
☐	☐	Appearance
☐	☐	Bathing / dressing
☐	☐	Breathing
☐	☐	Changes in urination
☐	☐	Constipation
☐	☐	Diarrhoea
☐	☐	Eating
☐	☐	Fatigue
☐	☐	Feeling swollen
☐	☐	Fevers
☐	☐	Getting around
☐	☐	Indigestion
☐	☐	Memory / concentration
☐	☐	Mouth sores
☐	☐	Nausea
☐	☐	Nose dry / congested
☐	☐	Pain
☐	☐	Sexual
☐	☐	Skin dry / itchy
☐	☐	Sleep
☐	☐	Tingling in hands / feet

Other problems

The Distress Thermometer

Introduction

"Distress is anything which impacts negatively upon your life and stops you from doing anything you enjoyed before your diagnosis"

Having a serious illness can impact on many aspects of a person's life. The physical challenges presented are often the most obvious and are the focus of any treatment. However, health professionals are also often well placed to advise people when dealing with other difficulties such as psychological, spiritual, social and practical.

For many reasons, we know that it can be difficult for both the health professionals and the person to discuss the broad range of challenges that some diseases present. The Distress Thermometer is a tool that can help both the person and staff to begin a conversation with each other about the wider range of difficulties, together with the services and resources that may be helpful in addressing them.

Instructions

How to Use the Distress Thermometer

There are many ways of using the Distress Thermometer. Most importantly it is a way of enhancing communication between people and their health care teams. It allows a whole range of concerns to be explored. As an individual you may find your own way of using the Distress Thermometer and sharing it with others. Listed below are three ways of using this measure.

1. ***Just circling a number***
You may find that you only want to do the first part of the tool, circling the number on the thermometer that best describes the distress you have felt over the past week. This is a quick way of identifying for yourself the extent of any distress that you may be experiencing.

2. ***Adapting the instructions***
After step 1 tick any problem boxes that apply to you. This can help you identify what has been contributing to your distress.

3. ***Following the full instructions***
Rank the top four problem areas. This can help you to identify which are the areas of greatest concern, providing a good starting point for developing a plan to address the concerns.

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Roche

V 0477

Beck Depression Inventory

CRTN: _____ CRF number: _____ Page 14 patient inits: _____

Baseline

BDI-II®

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness
- 0 I do not feel sad.
- 1 I feel sad much of the time.
- 2 I am sad all the time.
- 3 I am so sad or unhappy that I can't stand it.

2. Pessimism
- 0 I am not discouraged about my future.
- 1 I feel more discouraged about my future than I used to be.
- 2 I do not expect things to work out for me.
- 3 I feel my future is hopeless and will only get worse.

3. Past Failure
- 0 I do not feel like a failure.
- 1 I have failed more than I should have.
- 2 As I look back, I see a lot of failures.
- 3 I feel I am a total failure as a person.

4. Loss of Pleasure
- 0 I get as much pleasure as I ever did from the things I enjoy.
- 1 I don't enjoy things as much as I used to.
- 2 I get very little pleasure from the things I used to enjoy.
- 3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
- 0 I don't feel particularly guilty.
- 1 I feel guilty over many things I have done or should have done.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6. Punishment Feelings
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7. Self-Dislike
- 0 I feel the same about myself as ever.
- 1 I have lost confidence in myself.
- 2 I am disappointed in myself.
- 3 I dislike myself.

8. Self-Criticalness
- 0 I don't criticize or blame myself more than usual.
- 1 I am more critical of myself than I used to be.
- 2 I criticize myself for all of my faults.
- 3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10. Crying
- 0 I don't cry anymore than I used to.
- 1 I cry more than I used to.
- 2 I cry over every little thing.
- 3 I feel like crying, but I can't.

Subtotal Page 1

Continued on Back

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V 0477

Beck Depression Inventory

CRTN: _____ CRF number: _____

Baseline

Page 15 patient inits: _____

11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

3456789101112 ABCDE

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ROYAL FREE

SF 36 Short Form Survey Assessment Instrument

Developed at RAND as part of the Medical Outcomes Study

Hosp No _____ Date _____

Visit No 1 2 3

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. **Compared to one year ago**, how would your rate your health in general **now**?	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

(Circle One Number on Each Line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing **several** flights of stairs	[1]	[2]	[3]
7. Climbing **one** flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking **more than a mile**	[1]	[2]	[3]
10. Walking **several blocks**	[1]	[2]	[3]
11. Walking **one block**	[1]	[2]	[3]
12. Bathing or dressing yourself	[1]	[2]	[3]

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle One Number on Each Line)

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

(Circle One Number on Each Line)

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks,** to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(Circle One Number)

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

21. How much **bodily** pain have you had during the **past 4 weeks?**

(Circle One Number)

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

22. During the **past 4 weeks,** how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(Circle One Number)

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

These questions are about how you feel and how things have been with you **during the past 4 weeks.** For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks . . .**

(Circle One Number on Each Line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks,** how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

(Circle One Number)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

How TRUE or FALSE is each of the following statements for you?

(Circle One Number on Each Line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

Patient's Name _____ Date ___/___/___ ID # ____

MEMORIAL SYMPTOM ASSESSMENT SCALE – Short Form [MSAS-SF]

I. INSTRUCTIONS: Below is a list of symptoms. If you had the symptom DURING THE PAST WEEK, please check Yes. If you did have the symptom, please check the box that tells us how much the symptom DISTRESSED or BOTHERED you.

Check *all* the symptoms you have had during the PAST WEEK.	Yes [✓]	→→ IF YES: How much did it DISTRESS or BOTHER you? Not at All [0]	A little Bit [1]	Some-what [2]	Quite a Bit [3]	Very Much [4]
Difficulty concentrating						
Pain						
Lack of energy						
Cough						
Changes in skin						
Dry mouth						
Nausea						
Feeling drowsy						
Numbness/tingling in hands and feet						
Difficulty sleeping						
Feeling bloated						
Problems with urination						
Vomiting						
Shortness of breath						
Diarrhea						
Sweats						
Mouth sores						
Problems with sexual interest or activity						
Itching						
Lack of appetite						
Dizziness						
Difficulty swallowing						
Change in the way food tastes						
Weight loss						

1

Patient's Name _____ Date ___/___/___ ID # ____

MEMORIAL SYMPTOM ASSESSMENT SCALE – Short Form [MSAS-SF]

I. INSTRUCTIONS: Below is a list of symptoms. If you had the symptom DURING THE PAST WEEK, please check Yes. If you did have the symptom, please check the box that tells us how much the symptom DISTRESSED or BOTHERED you.

Check *all* the symptoms you have had during the PAST WEEK.	Yes [✓]	→→ IF YES: How much did it DISTRESS or BOTHER you? Not at All [0]	A little Bit [1]	Some-what [2]	Quite a Bit [3]	Very Much [4]
Hair loss						
Constipation						
Swelling of arms or legs						
"I don't look like myself"						
If you had any other symptoms during the PAST WEEK, please list them below, and indicate how much the symptom DISTRESSED or BOTHERED you. 1. _____						
2. _____						

II. Below are other commonly listed symptoms. Please indicate if you have had the symptom DURING THE PAST WEEK, and if so, how OFTEN it occurred.

Check *all* the symptoms you have had during the PAST WEEK	Yes [✓]	→→ IF YES, How OFTEN did it occur? Rarely [1]	Occasionally [2]	Frequently [3]	Almost Constantly [4]
Feeling sad					
Worrying					
Feeling irritable					
Feeling nervous					

13 Appendix C: Funding

1. KRUK Project Grant for “Validation of the Distress Thermometer in the UK Renal Population” 2013
2. UCL Grand Challenges Project Grant for “Distress in Older Renal Patients” interview study 2013
3. UCL Impact Studentship for PhD 2012

14 Appendix D: Posters, abstracts and publications arising from this thesis

Posters and Oral Presentations

1. Alston H. Validation of the Distress Thermometer in a UK Renal Population (oral presentation) British Renal Society Annual Conference 2015 – B**est Abstract prize**
2. Helen Alston, Victoria Vickerstaff, Joseph Low, Maria Da Silva Gane, Christine Beatty, Aine Burns. Haemodialysis Patients Experience Higher Levels of Depression and Psychosocial Distress than Equivalent CKD Patients (poster presentation). ASN Kidney Week 2014
3. Alston H, Burns A. Use of the distress thermometer in older renal patients – a pilot study (oral presentation) ASN Kidney Week, San Diego 2012 - **Dimitrios Oreopoulos/ASN Geriatric Nephrology Travel Award prize**
4. Hughes T, Alston H, Burns A. What Can Elderly Frail Patients with Advanced CKD Expect If They Elect Not To Undergo Dialysis? (poster presentation) ASN Kidney Week 2012
5. Alston H, What Prompts Initiation of Renal Replacement Therapy in Older Patients? (poster presentation) Renal Association Annual Conference 2012

Invited lectures

1. "Advance Care Planning for Renal Patients in the ITU" North East Intensive Care Society, Nov 2017
2. "The Distress Thermometer" Kings College Hospital Renal Dept academic meeting, Nov 2017
3. "Assessing patient outcomes – use of the Distress Thermometer in Older Renal Patients" Kidney Disease in Older People, Royal Society of Medicine, January 2017
4. "The Distress Thermometer in UK Renal Patients" Renal Supportive Care conference, Sept 2015
5. "The Management of Older Renal Patients" South Thames Renal Regional Training Day, April 2014

Publications

1. Alston H, Burns A, Davenport A. Loss of Appendicular muscle mass in haemodialysis patients is associated with increased self-reported depression, anxiety and lower general health scores. Nephrology 2017 May 25. doi: 10.1111/nep.13075. PMID: 28545164.
2. Alston H, Burns A. Conservative care of the patient with end-stage renal disease. Clinical Medicine (Lond). 2015 Dec; 15(6):567-70. doi:10.7861/clinmedicine.15-6-567. PMID: 26621950.
3. Alston, Helen, Burns, Aine. "Ageing Renal Patients: We Need More Collaboration between Geriatric Services and Nephrology Departments." Healthcare. 2015; 3(4): 1075-85. PMID: 27417814;
4. Alston H. “Conservative care for end-stage kidney disease: joint medical conference with the Renal Association, British Geriatrics Society and Association for Palliative Medicine”. Clin Med (Lond). 2013 Aug;13(4):383-6. doi:10.7861/clinmedicine.13-4-383. PMID: 23908510

15 Appendix E: List of training completed as part of this thesis

Presentation Skills Workshops - University College London
Term 3, 2012/13 - Workshop 2
Start Date: 01-05-2013 End Date: 09-05-2013

Library Skills Training for Science and Engineering Students - University College London
2012/13: Endnote
Start Date: 12-11-2012 End Date: 12-11-2012

Research Governance and IRAS Training - University College London
2012/13: Term 1
Start Date: 23-10-2012 End Date: 23-10-2012

Maximising Your Potential Part 1: Introduction to Skills Development and the Research Student Log - University College London
2012/13 - November Induction Session for Research Students and Supervisors
Start Date: 14-11-2012 End Date: 14-11-2012

Library Skills Training for the Biomedical Sciences - University College London
2012/13: Whose research gets noticed? Counting citations and why citations count
Start Date: 14-01-2013 End Date: 14-01-2013

Library Skills Training for the Biomedical Sciences - University College London
2012/13: Getting your paper published: a beginner's guide
Start Date: 24-01-2013 End Date: 24-01-2013

Statistical Analysis Methods for Epidemiology and Social Sciences - University College London
2012/13: Block 1
Start Date: 09-04-2013 End Date: 23-04-2013

Statistical Analysis Methods for Epidemiology and Social Sciences - University College London
2012/13: Block 2
Start Date: 30-04-2013 End Date: 07-05-2013

Statistical Analysis Methods for Epidemiology and Social Sciences - University College London
2012/13: Block 3
Start Date: 14-05-2013 End Date: 14-05-2013

Statistics for Researchers - University College London
2012/13 Design of Experiments
Start Date: 25-01-2013 End Date: 08-02-2013

Statistics for Researchers - University College London
2012/13 Observational Studies
Start Date: 11-01-2013 End Date: 18-01-2013

Library Skills Training for the Biomedical Sciences - University College London

2012/13: Advanced and systematic literature searching using biomedical databases
Start Date: 20-11-2012 End Date: 20-11-2012

Library Skills Training for the Biomedical Sciences - University College London
2012/13: Current awareness and keeping up to date
Start Date: 05-02-2013 End Date: 05-02-2013

Charting with Excel - University College London
2012/13: IS Training
Start Date: 26-11-2012 End Date: 26-11-2012

Statistics for Researchers - University College London
2012/13 Analysis of Data & Graphical Methods
Start Date: 22-02-2013 End Date: 08-03-2013

Statistical Analysis Methods for Epidemiology and Social Sciences - University College London
2012/13: Block 4
Start Date: 21-05-2013 End Date: 21-05-2013

Statistical Analysis Methods for Epidemiology and Social Sciences - University College London
2012/13: Block 5
Start Date: 04-06-2013 End Date: 11-06-2013

An Introduction to Semi-Structured Interviews - London School of Hygiene and Tropical Medicine
Spring 2013
Start Date: 23-01-2013 End Date: 23-01-2013

Introduction to Dealing with Missing Data (1 Day)

Start Date: 09-10-2013 End Date: 11-10-2013

Introduction to Survival Analysis

Start Date: 23-10-2013 End Date: 23-10-2013

Sample Size Estimation and Power Calculations

Start Date: 13-12-2013 End Date: 13-12-2013

Writing Across the Genres: for science and medicine PhDs - University College London
6 Feb 2014
Start Date: 06-02-2014 End Date: 06-02-2014

Skills for Conflict Resolution - University College London
7 and 14 July 2014
Start Date: 07-07-2014 End Date: 14-07-2014

Facilitation Skills Training - University College London
14, 18 and 21 Feb 2014

Start Date: 14-02-2014 End Date: 21-02-2014

Effective Negotiation Skills - University College London
27 May 2014
Start Date: 27-05-2014 End Date: 27-05-2014

Modern Languages at the UCL Centre for Languages & International Education (CLIE) - University College London
Log points Spanish
Start Date: 01-01-2013 End Date: 00-00-0000

Multilevel Modelling for Health Research - University College London
30 Mar-1 Apr 2015
Start Date: 30-03-2015 End Date: 01-04-2015

16 References

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