Fatigue and Disease Trajectories in Chronic Liver Disease Patients: The Role of Gender and Coexistent Symptoms

A DISSERTATION
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA
BY

Roberta Ann Jorgensen

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

Cynthia Gross, PhD, Advisor

August 2010
ACKNOWLEDGEMENTS

This research emanated from my interest in symptom manifestations in chronic disease, a long history of working with chronic liver disease patients in treatment trials and my own research in this area. My master’s thesis was a longitudinal study of quality of life in liver disease. My qualitative study of fatigue in women with primary biliary cirrhosis made me aware of the impact this symptom can have on patients’ lives. I became intrigued about advanced longitudinal methods which seemed to be an appropriate way to answer my research questions about the interrelatedness of fatigue and chronic liver disease.

My advisor Dr. Cynthia Gross has provided expert guidance, encouragement, and most importantly belief in my ability. I am fortunate and grateful to have had the opportunity to work with her and be the recipient of her mentorship.

I would like to acknowledge my dissertation committee members Drs. Joseph Gaugler, Patricia Frazier, and Kay Savik for their contributions as committee members and development of my research. I would like to acknowledge the contribution of Dr. Susan Henly who inspired in me a curiosity about the use of more advanced statistical methods to answer research questions in nursing.

I would like to acknowledge Dr. Keith Lindor at Mayo Clinic, the principal investigator of the original treatment trial, whose research provided me with this opportunity. I would like to acknowledge Dr. Patricia Robuck and the National Institute of Health (NIH) in their willingness to allow me to use these data for my dissertation.
DEDICATION

This research is dedicated to my husband Paul whose unwavering support and love made it possible for me to reach this important goal. I would like to thank my daughters Laura and Lyndsey who as young women are inspirational in their own right in their pursuit of careers in law. I would like to remember my mother and father who set examples of lifelong intellectual curiosity and academic achievement.

This research is dedicated to the patients with primary sclerosing cholangitis who suffer from a chronic progressive liver disease with yet no viable treatment options. Their willingness to partake in investigational drug trials and provision of important information on the impact of this devastating disease has made this research possible.
ABSTRACT

BACKGROUND: Fatigue is a common symptom in chronic liver disease, significantly impacting multiple aspects of quality of life. Although fatigue severity correlates poorly with traditional markers of liver disease activity, greater fatigue has been associated with an increased risk for early death, providing evidence of its prognostic significance (Jones, 2006). Gender differences exist in fatigue reporting yet little is known about gender differences in liver disease. Fatigue in liver disease has been associated with symptoms of sleep disturbance and daytime somnolence yet the relationship of these other symptoms with underlying disease is not well studied. The purpose of this study was to investigate the interrelatedness of fatigue and disease trajectories in patients with chronic liver disease. The intent of this analysis was to explore whether the general level and rate of change over time differs by gender and the presence at baseline of other symptoms.

METHOD: A secondary analysis was done of data collected on 150 primary sclerosing cholangitis (PSC) patients who participated in a treatment trial over a 5-year period. Patients completed yearly fatigue questionnaires and quality of life assessments, which included symptom questions, and were assessed on severity of their liver disease by calculation of risk scores. Linear mixed-effect models were used to examine patterns of fatigue and disease, their covariation over time, and the predictive effect of gender and coexistent symptoms.

RESULTS: Fatigue increases only slightly over time; yet liver disease severity exhibits an accelerated rate of progression. Female gender, insomnia, concentration difficulty, and itching predict significantly greater fatigue levels. Itching and disease duration were
related to disease severity. Although women suffer great fatigue morbidity they do not suffer worse disease. Levels and patterns of fatigue and disease severity do not covary over time, indicating that they are separate processes.

**CONCLUSIONS:** Fatigue levels in liver disease patients remain stable with little increase over time; however disease progresses at an increasing rate of change. Women and those with insomnia, concentration difficulty and itching are more likely to have greater fatigue but not worse disease. No evidence was found of an association between fatigue and disease levels or related patterns of change over time.
TABLE OF CONTENTS

Acknowledgments...........................................................................................................i
Dedication.........................................................................................................................ii
Abstract..........................................................................................................................iii
Table of Contents............................................................................................................v
List of Tables...................................................................................................................viii
List of Figures................................................................................................................ix
List of Appendices..........................................................................................................x

Chapter I: Introduction.................................................................................................1
  Problem Statement.........................................................................................................5
  Purpose of the Study......................................................................................................6
  Study Aims.....................................................................................................................6

Chapter II: Background and Review of the Literature...............................................8
  Fatigue in Chronic Liver Disease....................................................................................9
  Cholestatic Liver Disease...........................................................................................9
  Mechanisms of Fatigue...............................................................................................11
  Markers of Disease Severity.......................................................................................13
  Fatigue and Associated Factors in Chronic Liver Disease.........................................14
    Disease-related factors...............................................................................................14
    Fatigue and mortality risk..........................................................................................16
    Fatigue and psychological factors.............................................................................16
    Gender and fatigue in liver disease.........................................................................22
    Gender and disease....................................................................................................24
    Fatigue and coexistent symptoms..........................................................................25
  Measurement of Fatigue..............................................................................................26
  Fatigue, Disease, Gender, and Symptoms...................................................................27
  Conceptual Framework...............................................................................................28
  Research Questions and Hypotheses..........................................................................30

Chapter III: Methods...................................................................................................31
  Sample and Variables.................................................................................................31
  Study Design.................................................................................................................33
  Measures.......................................................................................................................34
    Fatigue measurement.................................................................................................34
    Liver disease severity...............................................................................................36
    Symptoms..................................................................................................................37
  Data..............................................................................................................................38
Data analysis................................................................................................................................39
Analysis for Aim 1................................................................................................................................40
Model selection for the covariance structure .................................................................................41
Analysis for Aim 2................................................................................................................................42
Analysis for Aim 3................................................................................................................................44
Analysis for Aim 4................................................................................................................................45
Missing Data.........................................................................................................................................48

Chapter IV: Results of Analyses.........................................................................................................51
Sample Characteristics......................................................................................................................51
Covariance structure..........................................................................................................................53
Research Question 1..........................................................................................................................54
  Unconditional means model for fatigue..........................................................................................56
  Unconditional means model for risk score.......................................................................................57
Research Question 2..........................................................................................................................59
  Multilevel model for fatigue change...............................................................................................59
  Multilevel model for disease change...............................................................................................60
Missing Data Pattern..........................................................................................................................61
Research Question 3..........................................................................................................................62
Research Question 4..........................................................................................................................63
  Multilevel model for bivariate linear change..................................................................................63
  Multilevel model for bivariate linear and quadratic change.........................................................64

Chapter V: Discussion..........................................................................................................................66
Demographics.......................................................................................................................................67
Patterns of Fatigue and Disease Severity..........................................................................................68
  Fatigue..............................................................................................................................................68
  Disease...........................................................................................................................................69
Gender and Symptoms as Predictors of Fatigue and Disease.........................................................70
  Gender and fatigue...........................................................................................................................70
  Gender and disease severity.............................................................................................................71
Co-existent symptoms and fatigue.....................................................................................................72
Co-existent symptoms and disease.....................................................................................................73
Missing Data Mechanism.....................................................................................................................74
Risk Score as a Time-varying Predictor of Fatigue............................................................................74
Relationship between Fatigue and Disease Trajectories.................................................................75
  Covariates in model for linear fatigue and disease change.........................................................75
  Covariation between linear fatigue and disease trajectories.......................................................76
  Covariates in model for linear fatigue and quadratic disease change.......................................77
  Covariation between linear fatigue and quadratic disease trajectories....................................78
Summary...............................................................................................................................................80
Strengths and Limitations...................................................................................................................81
  Strengths.........................................................................................................................................81
Limitations ..................................................................................................................... 81
Implications for Nursing .......................................................................................... 83
Implications for Future Research ............................................................................. 83

References .................................................................................................................. 85
Appendices ................................................................................................................ 124
List of Tables

Table 1. Example PSC Patients, Mayo Risk Scores, and Estimated Survival Probability ................................................................. 104

Table 2. Baseline Comparison of Study Patients and Remaining Original Trial Patients .......................................................................................................................... 105

Table 3. Means (SD), Sample Sizes, and Correlations on Fatigue Assessments over the 5-year period .................................................................................................................. 106

Table 4. Means (SD), Sample Sizes, and Correlations on the PSC Risk Scores over the 5-year period .......................................................................................................................... 107

Table 5. Unconditional Means and Growth Models for the Fatigue Data (n=135) ................................................................. 108

Table 6. Unconditional Means and Growth Models for the PSC Risk Score Data (n=135) .................................................................................................................................................. 109

Table 7. Comparison of (REML) log-likelihoods and AIC for the Covariance Pattern Models for Fatigue ........................................................................................................................................... 110

Table 8. Comparison of the (REML) log-likelihoods and AIC for the Covariance Pattern Models for PSC Risk Score Data ........................................................................................................................................ 111

Table 9. Linear Mixed Effect Model for Fatigue (n=135) ................................................................................................................................. 112

Table 10. Linear Mixed-Effect Model for PSC Risk Scores (n=135) ................................................................................................................................. 113

Table 11. Model for Fatigue with PSC Risk Score as a Time-Varying Covariate .................................................................................................................. 114

Table 12. Estimates of Fixed Effects for Multilevel Model of Linear Change in Fatigue and Disease ................................................................................................................................................................. 115

Table 13. Estimates of Random Effects for Multilevel Model of Linear Change in Fatigue and Disease ................................................................................................................................................................. 116

Table 14. Estimates of Fixed Effects for Multilevel Model of Linear Change in Fatigue and Quadratic Change in Disease ................................................................................................................................................................. 117

Table 15. Estimates of Random Effects for Multilevel Model of Linear Change in Fatigue and Quadratic Change in Disease ................................................................................................................................................................. 118
List of Figures

Figure 1. Fatigue Severity (Fatigue Impact Scores) over the 5-year period....................119
Figure 2. Disease Severity (Mayo Risk Score) over the 5-year period...........................120
Figure 3. Trellis Graphs of Fatigue Trajectories in a Subset of Patients.........................121
Figure 4. Trellis Graphs of Disease Trajectories in a Subset of Patients.........................122
Figure 5. Mean Standardized Scores for Fatigue and Disease Severity Outcomes........123
List of Appendices

Appendix A: Fatigue Impact Scale (FIS).................................................................124

Appendix B: Quality of Life Survey for Cholestatic Liver Disease (Chol-QOL)........131
CHAPTER 1

Introduction

Fatigue, perceived as a sense of overwhelming exhaustion and inability to perform usual activities, is ubiquitous in many chronic diseases. Fatigue is a multidimensional symptom that encompasses a range of complaints including lethargy, lassitude, malaise and exhaustion (Swain, 2006). It also occurs in healthy populations typically as acute fatigue, where it is self-limited, caused by an identifiable insult and relieved by appropriate rest (Piper, 1989). In contrast, chronic fatigue accompanies chronic illnesses where it lasts longer than 6 months, often has multiple or unknown causes, is not amenable to typical recuperative efforts and not related to exertion (Piper). Fatigue in healthy populations is defined as a state of weariness resulting from a period of mental or physical activity, yet this definition does not adequately describe fatigue in chronic disease where the degree of fatigue is out of proportion to previous activity. This fatigue is insidious in onset, cumulative and persistent, and rarely dissipated by sleep (Jorgensen, 2006). Fatigue is a complex symptom, defined as a persistent sense of exhaustion, inability to perform usual routine work, and a decreased capacity for physical and mental work (Barofsky, & Legro, 1991).

Chronic liver disease is a condition where fatigue is typically the most common complaint, although the exact prevalence varies by study and type of liver disease (Kumar & Tandon, 2002; Obermayer-Straub, Strassberg, & Manns, 2000; Poynard et al., 2002). Fatigue is particularly common in cholestatic liver diseases caused by
primary biliary cirrhosis and primary sclerosing cholangitis with prevalence statistics of 40 to 85%. (Huet, Deslauriers, Tran, Faucher, & Charbonneau, 2000; Zein & Lindor, 2001). Fatigue significantly impacts multiple aspects of quality of life (Sogolow, Lasker, & Short, 2008).

Fatigue in chronic conditions may be of peripheral origin as in conditions manifested by muscle wasting or joint inflammation such as rheumatoid arthritis and systemic lupus erythematosis, or central in origin (Swain, 2000). Fatigue in cholestatic liver disease is considered to be central rather than peripheral in origin with a number of potential causes proposed. Theories developed to explain central fatigue in chronic disease include the stress response related to the psychological impact of chronic disease and corticotrophin-releasing hormone (CRH), cytokine release as part of the immune response, alterations in central neurotransmission, and mood disorders (Swain).

Whether fatigue in liver disease is the result of depression is a point of contention. The search for underlying mechanisms in fatigue has evaluated the role of psychological factors, most commonly that of depression and anxiety resulting in variable findings (Cauch-Dudek, Abbey, Stewart, & Heathcote, 1998; Huet et al., 2000; Bjornsson, Simren, Olsson, & Chapman, 2004). Recently this association has been challenged on the basis that prevalence of depression in cholestatic liver disease is no higher than that seen in the general population, if assessed accurately (van Os, et al. 2007). In addition, treatment trials evaluating selective serotonin reuptake inhibitors have not been successful at alleviating fatigue in liver disease (ter Borg, van Os, van den Broek, & Hansen, 2004; Talwalkar, et al. 2006).
Fatigue correlates poorly with traditional markers of liver disease activity including biochemical tests and liver histology (Cauch-Dudek et al., 1998; Huet et al., 2000). Histological stage or the degree of fibrosis has not been associated with fatigue (Huet et al.; Blackburn, Freeston, Baker, Jones, & Newton, 2007), a finding potentially due to the problematic nature of histological stage as a marker (Bjornsson et al., 2004; Bjornsson, Simren, Olsson, & Chapman, 2005). Fatigue severity has been found to predict survival in patients with liver disease (Jones, et al. 2006), providing indirect evidence that there may be a relationship between fatigue and disease severity.

Few studies have examined whether fatigue in liver disease remains stable or increases over time. In one of two recent longitudinal studies of fatigue in cholestatic liver disease, scores were unchanged over a four-year period, yet increased levels were seen in those patients undergoing liver transplant and in those who died (Jones, et al. 2006). Bjornsson, et al. (2009) found similar findings in that high fatigue levels predicted liver related mortality and need for transplant in primary biliary cirrhosis patients. These studies provide evidence of an association between fatigue and liver disease severity.

The longitudinal course of cholestatic liver disease varies, occasionally presenting with periodic remissions and exacerbations (Zein & Lindor, 2001). The disease is characterized by progressive inflammatory destruction of bile ducts leading to cirrhosis and eventually liver failure over time. Observational cohort studies have shown that cholestatic liver disease and in particular, primary sclerosing cholangitis, is a
progressive disease, yet with subsets of patients who may follow different courses of disease progression (Talwalkar & Lindor, 2001).

Gender, an important factor in the understanding of illness, plays a significant role in symptom reporting (Clarke, 1999). Across multiple conditions, women report greater levels of fatigue and other symptoms than do men (Miaskowski, 2004; Husain, et al. 2007). Differences between men and women in disease symptoms, clinical presentation, and outcomes have been studied more extensively in heart disease (Artinian, & Duggen, 1995). Gender differences in fatigue have been studied somewhat in liver disease where women typically report greater levels of fatigue than do men (Piche, et al. 2001; Hilsabeck, Hassanein, & Perry, 2005).

Chronic liver disease, as in many other conditions is associated with multiple symptoms. In cholestatic liver disease, fatigue is the most common, followed by itching of the skin, jaundice, and abdominal pain (Charatcharoenwitthaya & Lindor, 2006). The recent development of a disease-specific quality of life instrument for cholestatic liver disease resulted in two discrete and unrelated symptom complexes focused on fatigue (together with cognitive and emotional dysfunction and other liver symptoms) and itching, with social dysfunction associated with both complexes (Newton, Bhal, Burt, & Jones, 2006). Additional research is needed to clarify the impact of multiple symptoms on fatigue, specifically whether a synergistic effect occurs that is predictive of a worse outcome.

The differential impact of disease-related morbidity by gender, and the paucity of research into the mechanisms behind these findings, indicates a need for a
longitudinal examination of these gender differences. Previous research has been primarily cross-sectional in design or if longitudinal limited to two time points. As fatigue in chronic disease is itself chronic, longitudinal research is needed to better understand the impact of this symptom and its relationship with disease, particularly how these co-vary.

**Problem Statement**

Fatigue is a distressing symptom of chronic liver disease with a significant impact on quality of life, yet factors associated with fatigue are poorly understood. The relationship between fatigue and depression in liver disease has been well substantiated in the literature, yet the actual prevalence of depression in liver disease has recently come under question (van Os, et al. 2007). In the majority of studies evaluating differences in fatigue by gender, women report greater severity, but no research exists on gender differences in liver disease severity. Patients with chronic liver disease suffer from other symptoms including itching, abdominal pain, and sleep disturbances yet it is unknown whether the presence of additional symptoms is associated with a perception of worse fatigue. Fatigue correlates poorly with disease severity, yet indicators of disease activity have often been measured at different time points or several years prior to the assessment of fatigue (Bjornsson et al., 2004) limiting conclusions about the relationship between fatigue and disease activity. To move this level of inquiry forward, fatigue and disease severity need to be measured as trajectories to then determine how they interrelate over time. The effect of gender and other symptoms as covariates will
help to determine their predictive role in fatigue trajectories. All of these factors have implications for screening and treatment interventions.

**Purpose of the Study**

The purpose of this study was to investigate whether trajectories of fatigue are related to trajectories of disease severity in patients with chronic liver disease. Patterns of the interrelatedness of fatigue symptoms and disease severity will be determined. The intent of this analysis is to explore whether the general level and rate of change over time differs by gender and the presence at baseline of other symptoms.

**Study Aims**

The primary aims and hypotheses of this research include:

**Aim 1**: To examine the trajectories of fatigue and disease severity in patients with chronic liver disease over a period of up to 5 years.

  **Hypothesis 1**: Patients with chronic liver disease will exhibit linear increases in both fatigue and disease severity over time.

**Aim 2**: To examine whether these fatigue and disease trajectories differ by gender and by co-existent symptoms at baseline.

  **Hypothesis 2.1**: Female gender and presence of symptoms at baseline will predict greater initial fatigue levels.

  **Hypothesis 2.2**: Male gender and presence of coexistent symptoms at baseline will predict greater initial disease severity.

**Aim 3**: To determine whether disease severity as a time varying covariate predicts changes in fatigue severity over time.
Hypothesis 3.1 Varying values in disease severity will predict changes in fatigue severity over time with adjustment for static covariates.

Aim 4: To determine whether patterns of fatigue and disease severity in chronic liver disease patients co-vary together over time.

Hypothesis 4: Fatigue and disease patterns will be correlated over time.
CHAPTER TWO

Background and Review of the Literature

Fatigue is a common experience in illness and health, yet is complex and multifaceted, involving interactions between biological, psychosocial and behavioral processes. In healthy states, fatigue is a normal occurrence after strenuous physical exertion or periods of inadequate sleep, and is alleviated by typical restorative efforts. Fatigue in healthy states is predictable, protective and resolves quickly, contrasted with fatigue in chronic illness which is abnormal and excessive, with an insidious onset yet persistent over time, not explained by activity and not relieved by typical restorative measures (Piper, 1989). Fatigue unrelated to physical activity, not restored by typical recuperative efforts, and unrelenting in nature, becomes a symptom. As such it is found in a large proportion of those with chronic health conditions such as cancer, heart failure, irritable bowel syndrome, multiple sclerosis, and liver disease (Cella, Davis, Breitbart, & Curt, 2001; Falk, Swedberg, Gaston-Johansson & Ekman, 2007; Piche et al., 2002; Chwastiak et al., 2005; Jones et al. 2006).

An appropriate classification of fatigue has been based on its theorized origin - that of a central versus peripheral origin, central being the theorized origin in chronic disease (Piper, 1989). Peripheral fatigue results from neuromuscular dysfunction outside the central nervous system (CNS) and results in impaired neurotransmission in peripheral nerves (Swain, 2000). Central fatigue implies altered neurotransmission
pathways within the CNS and often co-exists with psychological complaints (Aaronson et al., 1999)

**Fatigue in Chronic Liver Disease**

Chronic liver disease was ranked as the 7th leading cause of death among Americans 35-44 and was the 4th leading cause of death among those 45-54 years of age in 2006 (CDC/NCHS National Vital Statistics System [http://www.cdc.gov/nchs/deaths.htm](http://www.cdc.gov/nchs/deaths.htm)). Fatigue is a prominent symptom in patients with chronic liver disease particularly those with chronic hepatitis C and the cholestatic liver diseases primary biliary cirrhosis and primary cirrhosis. Fatigue affects patients with chronic hepatitis C at prevalence rates between 50 and 75% (Poynard et al., 2002; Kallman et al., 2007). In chronic hepatitis fatigue is often associated with depression (Dwight et al., 2000; Poynard et al.). Fatigue occurs in up to 85% of patients with primary biliary cirrhosis and is considered the worst symptom by 50% of those patients (Huet et al., 2000). Fatigue in primary sclerosing cholangitis has not been studied as extensively, but prevalence rates are reported to be as high as 75% (Zein & Lindor, 2001). Fatigue in cholestatic liver disease significantly impacts quality of life, interfering with physical activity, family life, and job performance (Sogolow et al., 2008; Witt-Sullivan et al., 1990).

**Cholestatic Liver Disease**

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are considered cholestatic liver diseases as these diseases share the common feature of bile stasis resulting from bile duct strictures within the liver (PBC) or in those also external to the liver (PSC) (Angulo & Lindor, 1999). These diseases follow a slowly progressive
course as the result of an immune-mediated destruction of bile ducts. Approximately 90% of patients with PBC are female (Kaplan & Gershwin, 2005) with a U.S. age-adjusted prevalence rate of 40.2 per 100,000 persons as of 1995 (Kim et al., 2000). PBC is characterized by slow progression but a highly variable course. A large cohort study of patients with PBC has shown that the median survival or liver transplantation referral from diagnosis was 9.3 years (Prince, Chetwynd, Newman, Metcalf, & James, 2002).

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease with a pathogenesis similar to PBC, but with a male predilection at 60% and common co-morbidity of inflammatory bowel disease (Charatcharoenwitthaya & Lindor, 2006). PSC affects patients in their third to fourth decade of life (Lee & Kaplan, 1995; Sherlock, 2000). Symptoms of PSC include progressive fatigue, pruritus, and jaundice (Zein & Lindor, 2001). Although onset of the disease may be insidious and the clinical course variable, progressive obliteration of bile ducts leads to biliary cirrhosis, portal hypertension with complications including bleeding from varices (dilated blood vessels in the esophagus) and liver failure (Wiesner, Grambsch, & Dickson, 1989). PSC is the 4th most common indication for liver transplantation, the only known effective treatment, yet PSC reoccurs in up to 20% of patients post transplant (Wiesner, 2001). The prevalence of PSC in the United States was found to be 13.6 per 100,000 persons, a prevalence that with its attendant medical burdens, was found to be significantly greater than previously estimated (Bambha et al., 2003).
Mechanisms of Fatigue

The etiology of fatigue in liver disease is elusive. It has been studied to a greater degree in primary biliary cirrhosis than in primary sclerosing cholangitis; however, proposed etiologies both relate to the similar “cholestatic” nature of these diseases. There is evidence that this fatigue is of a centrally mediated rather than peripheral origin, substantiated by the limited studies of cholestasis and in animal models of cholestasis (Swain & Maric, 1995).

Central fatigue originates within the central nervous system (CNS) and is associated with greater perceived effort when performing tasks (Chaudhauri & Behan, 2004) providing evidence that central fatigue results from altered neurotransmission within the brain (Swain, 2006). Although fatigue does not correlate well with markers of disease activity in patients with liver disease, it is associated with symptoms of depression and anxiety, which are also related to altered neurotransmission within the central nervous system (Huet et al., 2000; Bjornsson et al., 2004).

Hypothesized alterations in neurotransmission involve corticotropin-releasing hormone (CRH), serotoninergic [5-hydroxytryptamine (5-HT)], noradrenaline and other neurotransmitter systems (Swain, 2006). Behaviors consistent with defective central CRH release have been documented in animal models of cholestatic liver disease (Swain & Maric, 1995). Abnormal serotoninergic neurotransmission has been associated with fatigue in that increased central serotonin levels may result in central fatigue (Lucki, 1998). It was found that a 5HT receptor agonist which desensitizes 5HT autoreceptors and increases serotonin release into synapses where receptors are active
ameliorated fatigue-like behaviors in animal models of cholestatic liver disease (Nguyen, et al. 2008). However, studies evaluating 5HT receptor antagonists (including Fluvoxamine) in liver disease associated fatigue showed equivocal results (Jones, 1999; Theal, Toosi, & Girlan, 2005). Therefore, the role of serotonin in liver disease-associated fatigue remains controversial.

Questions about the role of other neurotransmitters in the genesis of fatigue have been raised. Altered central cytokine responses in animal models of liver disease have suggested that cytokines (large proteins) entering or produced within the brain can induce fatigue in the setting of liver disease (Swain, Beck, Rioux, & Let, 1998). It is theorized there may be a direct communication pathway between the liver and the brain in the role of fatigue, via neural (nerve projections) or humoral (substances contained in circulation) pathways (Swain, 2006). There may be reason to question this theory as recurrence of severe fatigue occurs in 50% of patients after liver transplantation (van den Berg-Emons, et al. 2006). A pathophysiologic basis for liver disease-related fatigue is unverified.

The role of amino acids in liver disease associated fatigue was investigated due to evidence of a relationship with fatigue in several non-hepatological conditions. Ter Borg, Fekkes, Vrolijk, and van Buuren (2005) aimed to identify the relationship of amino acid patterns to cholestatic liver disease-related fatigue. Several amino acids including valine, isoleucine, and leucine were significantly decreased in both PBC and PSC compared with 73 healthy controls. PBC patients with increased levels of the amino acid tyrosine had less fatigue (p = .01); no significant correlations between amino
acids and fatigue were found in PSC patients. The authors had no explanation for the differential findings in PBC and PSC, as it is likely that fatigue would have a similar etiology in both diseases.

**Markers of Disease Severity**

In an attempt to determine whether fatigue symptoms relate to the severity of underlying liver disease a number of markers have been evaluated. Chronic liver disease generally runs a steady course with phases of improvement and deterioration, yet with an overall slow rate of progression; these indicators are theorized to reflect the state where the disease is at in this progression (Christensen, 2004). Histologic stage of liver disease is a common marker and measured by needle extraction of liver tissue. These biopsies are typically staged according to the degree of fibrosis on a four-point scale with stage four indicating more advanced disease and evidence of cirrhosis (Ludwig, Czaja, Dickson, LaRusso, & Wiesner, 1984). Accurate staging is difficult as stage of disease may vary in severity according to from where the sample of liver tissue is taken (Zein & Lindor, 2001). Liver biopsy is associated with significant morbidity, which limits the frequency with which it is performed (Burak, Angulo, & Lindor, 2003). Natural history models no longer require histologic stage to predict outcomes in cholestatic liver diseases, making liver biopsy primarily used for diagnostic purposes (Burak et al.). Liver enzymes including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) measure the intensity of the disease process and are useful indicators in early stage disease. In more advanced disease, prothrombin time (clotting time), serum bilirubin (level of jaundice) and serum
albumin (a protein the liver synthesizes) are more useful as indicators of disease severity (Christensen).

Prognostic models combining clinical and biochemical information have been used to represent disease severity in studies of fatigue and liver disease. The Mayo risk score is a model consisting of biochemical and clinical data developed to predict survival and determine appropriate timing of liver transplantation in patients with primary biliary cirrhosis (Dickson, Grambsch, Fleming, Fisher, & Langworthy, 1989) and later adapted to patients with primary sclerosing cholangitis (Kim et al., 2000). The model has been extra-murally cross-validated and has been shown to correlate well with estimated and actual survival of PSC patients (Wiesner et al., 1989). Disease severity has also been measured by use of the Child-Pugh model, which is a composite of bilirubin, albumin, clotting time, ascites (fluid in the abdomen), and encephalopathy (a state of altered consciousness in advanced liver disease) (Pugh, Murray-Lyon, Dawson, Pietroni, & Williams, 1973).

**Fatigue and Associated Factors in Chronic Liver Disease**

Fatigue in chronic liver disease is a subjective multidimensional symptom with a number of likely determinants. Studies have focused primarily on fatigue and liver disease-related pathophysiologic changes, psychological and coping factors, gender, and the role of fatigue-related symptoms.

**Disease-related factors**

Research studies evaluating the role of disease activity in fatigue are reviewed here. Relationships were found between fatigue and markers of disease severity in
studies of viral hepatitis patients. In a cross-sectional study of 215 patients with chronic hepatitis C, the relationship between fatigue and disease markers was evaluated (Teuber et al., 2008). Level of fatigue was measured by the Fatigue Impact Scale (FIS), which is a 40-item, 4-point Likert scale instrument including cognitive, psychosocial, and physical domains of fatigue with a score range of 0 to 160. Liver biopsies were graded on degree of fibrosis and according to the histologic activity index (HAI) scale. Fatigue was significantly greater in patients with advanced fibrosis ($p = .04$) when compared with those without fibrosis. Females were significantly more impaired with fatigue than males ($p = .007$). In multiple linear regression analysis fibrosis ($p = .04$) and gender ($p = .017$) were independent predictors of impairment in FIS score.

Additional evidence of a relationship between fatigue and liver disease severity was seen in a study of 1614 patients with hepatitis C (Poynard et al., 2002). Fatigue was measured by a 3-point grading scale, depression was measured as the presence of depression requiring anti-depressant medication, and liver biopsies (when performed) were graded on a 4-point scale from 0 (no fibrosis) to 4 (cirrhosis). Fatigue was associated with advanced fibrosis or cirrhosis ($p < .001$), female gender ($p < .006$), and depression ($p < .001$).

In a study of 115 patients with chronic hepatitis C, smaller correlations were found between fatigue as measured by the FIS and degree of fibrosis ($r = .25, p < .03$). Fatigue did not correlate well with biochemical tests (ALT and AST) but was related to levels of psychopathology including depression, anxiety, somatization and hostility (McDonald, Jayasuriya, Bindley, Gonsalvez, & Gluseska, 2002).
These studies would appear to support a disease related basis for fatigue in liver disease.

**Fatigue and mortality risk**

Further evidence that fatigue may be somehow related to disease is seen in the association between fatigue and risk of early death. In one of the few longitudinal studies of fatigue in liver disease, 139 patients completed an initial FIS for fatigue. Of these patients, the 108 patients who were alive four years later were re-surveyed (Jones et al., 2006). For the purposes of this study, patients were classified as high-fatigue (FIS > 40) or low-fatigue (FIS < 40). Of the original 139 patients, the high-fatigue patients at baseline had a significantly increased risk of death during the follow-up period over those classified as low-fatigue ($p = .006$). Fatigue was found to be an independent predictor of mortality. Fatigue levels in the surviving patients were not significantly different four years later. Similar findings were reported in a retrospective study of 241 primary biliary cirrhosis patients (Zein & McCullough, 2007). Self-reported fatigue at the time of initial evaluation was recorded. Patients who reported fatigue at initial presentation were significantly more likely to die during the mean follow-up period of 5.4 years. The presence of fatigue was not an independent predictor of mortality at follow-up, which the authors theorized might have been due to the lack of quantitative assessment of fatigue and the retrospective design.

**Fatigue and psychological factors**

In other studies fatigue was not associated with liver disease severity but was associated with psychopathology; these will now be reviewed. In a study of 94 patients
with chronic hepatitis C, fatigue was measured by the Multidimensional Assessment of Fatigue (MAF) which is a 16-item scale measuring four dimensions of fatigue including severity, distress, degree of interference in daily activities, and timing (Hilsabeck, Hassanein, & Perry 2005). In this study fatigue was related to depression ($r = .67, p < .001$) and female gender ($r = .24, p = .02$) but no relationship was found between fatigue and degree of liver fibrosis.

Cauch-Dudek et al. (1998) studied the relationship of fatigue with depression, sleep, and disease severity in 137 patients with primary biliary cirrhosis. Fatigue was measured by use of the Fatigue Assessment Instrument (FAI), a 29-item instrument. Depression was measured by use of the Hamilton Depression Rating Scale (HDRS) and the Center for Epidemiological Studies Depression Rating Scale (CES-D). Sleep quality was measured by the Pittsburgh Sleep Quality Index (PSQI), and Mayo risk score was used as a measure of disease severity. Patients reporting fatigue had significantly more depressive symptomatology than those not reporting fatigue on both the HDRS ($r = .53, p = .0001$) and the CES-D ($r = .46, p = .0001$) depression scales. Fatigued patients reported more impairment in sleep quality, more sleep disturbance, and daytime cognitive dysfunction than non-fatigued patients. FAI scores did not correlate with age, duration of disease, serum bilirubin or Mayo risk score.

Blackburn et al. (2007) explored psychological factors and coping strategies in fatigued PBC patients. Patients completed the PBC-40 (a quality of life scale that includes fatigue sub-domains), the Penn State Worry Questionnaire (measures degree of habitual worry), and the Hospital Anxiety and Depression Scale (HADS) which
measures current anxiety and depression. Patients were allocated into low fatigue and high fatigue groups. No differences were seen between the low and high fatigue groups regarding age, presence of cirrhosis on biopsy, and disease duration. Patients in the high-fatigue group were significantly more anxious \((p = .008)\), more depressed \((p < .001)\), and more likely to worry \((p < .05)\) than those in the low fatigue group.

Similar findings resulted from a study of fatigue, co-morbidities, and depression in 49 PBC patients (Biagini et al., 2008). The FIS, the Modified FIS (MFIS) and the Fatigue Severity Scale (FSS) were used to measure fatigue. Depression was measured by the Rand Medical Outcomes Study (MOS) Depression Screener, which is an 8-item instrument to screen depressive disorders (major depression and dysthymia). Depressed patients were found to be more fatigued than non-depressed patients, a difference that was not significant; however, the presence of co-morbidities was independently associated with higher fatigue scores \((p < .05)\). No significant correlation was found between fatigue scores and age, biochemical data, or histological stage.

Bjornsson et al. (2004) studied the relationship between fatigue, psychological factors, and disease in 83 patients with PSC. Fatigue was measured by the FIS, psychological well-being was measured by the Psychological Well-Being (PGWB) index, and depression was measured by the Beck Depression Inventory (BDI). Disease severity was measured by degree of fibrosis on liver biopsies, performed between 3 and 5 years prior to the study. A positive correlation was found between fatigue and depression \((r = .81, p < .001)\). A negative correlation was found between fatigue and total PGWB score \((r = -.77, p < .001)\). Depression and low general health were found to
be independent predictors for fatigue in PSC. Although no relationship between fatigue
and liver disease was found, the authors acknowledged that since only half (45%) had
undergone a liver biopsy within three years of the study they could not exclude the
impact of liver disease on fatigue.

Huet et al. (2000) found a high rate of fatigue in their study of PBC. Of the 126
patients in the study, 99 or 85.3% suffered from fatigue, which was considered the
worst symptom in 50.9% of patients. Patients completed the FIS, BDI, and the
Symptom Checklist (SCL) to evaluate their mental health. Liver biopsies available from
time of initial PBC diagnosis were reviewed for assessment of histologic stage.
Depression, defined as a BDI > 10, was found in 52 (44.8%) patients. Significant
correlations were found between the FIS and SCL ($r = .71, p < .0001$), and between the
FIS and BDI ($r = .81, p < .0001$). No correlation was found between FIS scores and
liver biochemical tests. No differences in fatigue were found between male and female
patients, nor was there a difference between patients more or less than 50 years of age.
A multiple regression analysis found that disease duration, presence of itching, Mayo
risk score, and histologic stage were not significant predictors of FIS scores.

Goldblatt et al. (2002) studied fatigue in 136 PBC patients, 11 of who had
undergone liver transplantation. Fatigue was measured by the FIS, and depression was
measured by the Rand MOS Depression Screener. Disease severity was measured by
use of the Child’s Pugh score; scores range from 5 – 10 with higher scores indicating
more advanced disease. No relationship with fatigue was found for any parameter of
disease activity including liver biochemical tests, Mayo risk score, and pruritus. No
difference was seen between the fatigue scores in the PBC patients with Child’s Pugh scores of 5 and Childs-Pugh scores > 5.

Although these studies indicate that psychopathology is a contributing factor in fatigue, this interpretation has recently been challenged. The use of depression instruments weighted toward the physical manifestations of depression may significantly skew results in patients with physical disease. Jones et al. (2007) noted that the depression tools used were not developed for assessing depressive symptoms in chronic illness and that their application in fatigue-associated disease may result in a capture of physical symptoms and misinterpretation of the presence of these features as being suggestive of depression resulting in a largely spurious correlation.

Further evidence of the questionable validity of depression instruments in chronic disease can be seen in a study by van Os (2007). Fifty-five consecutive PBC and 37 consecutive PSC patients underwent initial assessment using the Beck Depression Inventory (BDI). In the patient groups, 21 of the 55 PBC patients (38%), and 13 of the 37 PSC patients (35%) had a BDI score of greater than 10, a score regarded as being indicative of depression. The percentages of PBC and PSC patients meeting the criteria for depression in this study are similar to that in other studies of fatigue (Huet et al., 2000). The 34 patients meeting the cutoff of 10 for the BDI then underwent a formal structured psychiatric interview to assess for the presence of DSM IV criteria for depressive illness. Of the 21 PBC patients meeting the cutoff for depression (BDI > 10), only 2 or 9.5% of patients actually had depression according to the DSM IV criteria and 1 out of 13 of the PSC patients (8%) met the criteria for
depression. The use of depression instruments meant to measure the severity of a depressive disorder and not to determine the diagnosis of a depressive disorder may explain the findings in studies linking depression and fatigue (van Os et al.). Although the presence of a BDI score of > 10 was frequent in these patients, the predictive value of the BDI has been questioned. The BDI in the setting of PBC and PSC may be sensing processes that are associated with chronic disease including fatigue, insomnia, and loss of concentration (Jones, 2007). It would appear that fatigue is not as it may have appeared in previous studies simply the consequence of a depressive illness. Further evidence for this is seen in the ineffectiveness of anti-depressant medications in the treatment of fatigue in these liver diseases (ter Borg et al., 2004; Talwalkar et al., 2006).

The psychological and physical stressors related to chronic liver disease have been implicated in the genesis of fatigue in these conditions (Swain, 2006). Moreover these stressors have been implicated in changes in neurotransmitter systems (Chrousos & Gold, 1992), which may have a role in fatigue as previously discussed. Liver disease can be viewed as both a physical and psychological stressor for patients dealing with the stigma of liver disease (Fahey, 1999) and contribute to central fatigue. However, this does not account for the fact that a significant proportion of patients with liver disease seek medical care for complaints of fatigue prior to being diagnosed with liver disease. The role of psychological factors in fatigue is controversial and may be an impossible challenge to clarify.


**Gender and fatigue in liver disease**

Gender has been linked with fatigue in liver disease in that women consistently report greater fatigue than men. In a study of 78 chronic hepatitis C and 13 PBC patients, fatigue was considered by these patients to be their worst symptom (Piche et al., 2002). Fatigue as measured by the FIS did not correlate with liver biochemical tests, or with histologic stage of disease in these patients, but was found to be significantly worse in female patients ($p = .003$).

Several other studies in purely hepatitis C populations found relationships of fatigue with female gender. In a study of 120 patients, fatigue was measured by the FIS and the Brief Fatigue Inventory (BFI), which is a 9-item screening instrument for fatigue (Kramer et al., 2005). Fatigue was not related to the severity of hepatitis, but was related to gender. Women in this study reported greater levels of fatigue than men on both the FIS ($58$ vs. $44$, $p = .05$) and the BFI ($3.5$ vs. $2.4$, $p = .04$). Female gender was also associated with fatigue ($r = .25$, $p = .02$) in a study of 120 chronic hepatitis C patients (Hilsabeck et al., 2005). The primary finding was that social functioning was the most significant predictor of fatigue followed by depression and gender. Teuber et al. (2008) and Poynard et al. (2002) also found greater fatigue levels in women with chronic hepatitis C in their studies. The severity of fatigue in patients after liver transplantation was also found to be greater in women than men ($p = .01$), a difference not explained by older age or disabilities (van-den Berg-Èmons, 2006).

One study did not find a relationship with fatigue and gender. In a study of 16 PBC and 12 hepatitis C patients, FIS scores were significantly increased when
compared with controls ($p < .01$), yet no relationship was found between fatigue and gender (Ahboucha et al., 2008) perhaps due to the small number of patients studied.

It is noteworthy that no study in liver disease could be found reporting greater fatigue in men. Primary biliary cirrhosis, which has an overwhelming female preponderance of 90%, is a liver disease associated with a prevalence of fatigue as high as 80% (Huet et al., 2000). Greater reports of fatigue and other symptoms by women have been noted in other chronic conditions including rheumatoid arthritis (Huyser et al., 1998; Mancusco, Rincon, Sayles, & Paget, 2006), AIDS (Breitbart, McDonald, Rosenfeld, Monkman, & Passik, 1998; Voss, 2004), functional GI disorders (Simren, Svedlund, Posserud, Bjorndal, & Abrahamsson, 2008) and renal failure (Liu, 2005). Despite the frequency of this finding, few studies have evaluated and explored gender differences in symptom reporting in any depth. In one of the few studies to do so, female palliative care patients with advanced illness were found to experience a higher prevalence and greater severity of fatigue over the three-month period ($p < .005$), even when controlling for functional performance, depression and education (Husain et al., 2007).

A number of proposed theories exist for these differences including the way men and women deal with symptoms and stress, and different social positions of men and women in society (Bensing, Hulsman, & Schreurs, 1999). Psychological studies show women to have higher symptom reports than men particularly when measured in retrospect, differences that may arise from early socialization, greater female attentiveness to bodily cues and a greater willingness in females to report the symptoms
they perceive to others (Gijsbers van Wijk & Kolk, 1997). Whether these differences in symptoms arise from excess physical morbidity or merely differences in the way men and report symptoms is not evident. Regardless of whether differences in reported fatigue are of a psychosocial origin, it is important to also determine whether there are gender-specific ways in which men and women experience disease. This has not been studied in liver disease patients and seldom researched in other conditions.

Gender and disease

Paradoxically, women have been reported to suffer more symptom morbidity while men suffer greater disease mortality (Verbrugge, 1985). Women describe more physical symptoms than do men even in primary care settings (Gijsbers van Wijk, Huisman, & Kolk, 1999). Whether this translates into actual differences in pathophysiology and disease manifestations between men and women is not known. Studies have evaluated gender differences in fatigue and pain in cancer patients (Miaskowski, 2004), and in quality of life in patients with cardiac disease (Forthofer, Janz, Dodge, & Clark, 2001) and inflammatory bowel disease (Casellas, Lopez-Vivancos, Casado, & Malagelada, 2002). Yet little is known as to whether these differences in subjective measures of health status are accompanied by differences in underlying disease manifestations in men and women. A study of the clinical presentation in PSC patients showed that symptoms at diagnosis, predominantly itching, were more frequent in women than in men. No differences were seen in disease parameters including the presence of cirrhosis, or gastrointestinal bleeding, between men and women (Bergquist, Said, & Broome, 2007).
Fatigue and coexistent symptoms

Other symptoms occur in liver disease. In addition to fatigue, cholestatic liver disease is often associated pruritus or itching of the skin (Mendes & Lindor, 2004). This itching can be mild, moderate or extremely severe, interfering with sleep, resulting in skin excoriation, and even promoting suicidal ideation (Younossi, Kiwi, Bopari, Price, & Guyatt, 2000). No completely effective therapies exist and no pathogenesis has been established. Although this itching was previously thought to arise peripherally as a consequence of interactions between nerve endings in the skin and one or more substances that accumulate as a consequence of decreased liver function, this assumption is currently not supported by convincing data (Jones & Bergasa, 1999). Other evidence suggests that central events in the brain, specifically an increase in neurotransmission and neuromodulation which is mediated by endogenous opioid agonists, has been implicated (Bergasa & Jones, 1995). It has been suggested that the pruritus of cholestatic liver disease may be due to altered serotonergic neurotransmission (Schorer, Hartmann, & Ramadori, 1995), an area also proposed as a factor in fatigue in cholestatic liver disease (Jones & Bergasa). Despite the potential for significant itch-induced sleep disruption, itching and fatigue have not been consistently linked, and seldom investigated. Itching was found to be associated with fatigue severity in some studies (Poynard et al., 2002) yet not in others (Huet et al., 2000; Goldblatt, et al., 2002) in the few studies where it has been examined.

Abnormalities in sleep patterns and excessive daytime somnolence have been associated with fatigue in cholestatic liver disease (Cauch-Dudek et al., 1998). Patients
with fatigue reported difficulty initiating sleep, poor sleep quality, increased sleep disturbances and daytime cognitive dysfunction when compared with non-fatigued liver disease patients and controls. The degree of itch reported by patients was not found to correlate with sleep disturbance. Similarly, Newton, Gibson, Tomlinson, Wilton, and Jones (2006) reported that liver disease patients experienced a significant reduction in actual nighttime sleep despite a significant increase in daytime sleep when compared with controls. The presence of itch in these patients did not play a role in sleep quality. Itching has been postulated to reflect the presence of a central nervous system process occurring as a result of chronic inflammation and cholestasis (Newton, Pairman, Sutcliffe, Wilton, & Jones, 2008). In cholestatic liver disease, fatigue has been associated with cognitive dysfunction, which has been proposed as part of a symptom complex including emotional and social domains of quality of life (Newton et al., 2006). The relationship between sleep abnormalities, cognitive impairment, fatigue, and itching may have a common central origin and evidence suggests they may be related. This is not surprising as seldom are symptoms in chronic disease experienced in isolation.

**Measurement of Fatigue**

The increased recognition of fatigue as an important subjectively experienced symptom has resulted in a shift from physician-reported to patient-completed fatigue assessments and a move away from a simple present-versus-absent assessment of fatigue (Newton, Pairman, Sutcliffe, Wilton, & Jones, 2008). In comparisons with historical reviews of fatigue, the prevalence of fatigue in recent studies may seem
higher reflecting recognition of the importance of this symptom to patients (Newton, 2008). Interview based studies have revealed that even though patients with chronic disease label their sensation as fatigue, they find it qualitatively very different from the fatigue they experienced before they became ill (Glaus, Crowe, & Hammond, 1996). Due to findings such as this, a multi-dimensional approach might be better rather than measurement on a simple continuum, at capturing characteristics and manifestations of fatigue and its impact. A multidimensional fatigue instrument used commonly in liver disease is the Fatigue Impact Scale (FIS), which includes cognitive, physical, and psychosocial domains (Fisk et al., 1994).

**Fatigue, Disease, Gender and Symptoms**

Although the literature review included numerous studies citing depression and other psychopathology as causal factors in fatigue, these interpretations have recently come under question. Clearly a diagnosis of depression in liver disease as disparate from fatigue may be a challenge due to the overlap in manifested symptoms. Use of depression instruments may not be sufficient to discern true depression in these patients. Despite little evidence in support of a disease-based cause for fatigue, evidence that fatigue predicts early mortality in these patients raises again the possibility of a link. Consideration of gender differences in fatigue is important yet further investigation into underlying mechanisms for this has not been done. The cross-sectional design of the studies conducted limits causal inferences regarding the relationship between fatigue and disease, the role of gender and symptoms. Longitudinal research is needed to answer questions of how these factors relate over time.
Conceptual Framework

The conceptual framework for this study will incorporate factors identified in the review of literature on this topic and the questions still remaining. The model proposes that fatigue severity and indicators of disease will co-vary over time. Female gender will be associated with greater fatigue, yet men may suffer worse disease. The chronicity of fatigue and liver disease requires a longitudinal design, hence time is included. Little is known about the natural history of fatigue in chronic liver disease and less is known about how the course of fatigue correlates with the course of disease.

Despite inconclusive findings in the literature on the effect of itching on fatigue, there is theoretical justification for inclusion of it in the model. Other symptoms reported to occur in relationship with fatigue in liver disease are sleep difficulties, daytime somnolence and cognitive dysfunction. The relationships between these variables are depicted in the conceptual framework.
Figure 1: Conceptual Framework

Coexistent symptoms:
- Itching
- Insomnia
- Concentration

Gender

Fatigue

Disease Duration

Disease Severity

Fatigue Trajectory

Disease Trajectory

Time
Research Questions and Hypotheses:

The research questions and hypotheses of this research are:

**Research question 1:** What is the pattern of change in fatigue and disease severity in chronic liver disease patients over a 5-year period?

**Hypothesis 1:** Patients with chronic liver disease will exhibit linear increases in both fatigue and disease severity over time.

**Research question 2:** Do fatigue and disease trajectories differ by gender and by co-existent symptoms at baseline?

**Hypothesis 2.1:** Female gender and presence of symptoms at baseline will predict greater initial fatigue levels.

**Hypothesis 2.2:** Male gender and presence of coexistent symptoms at baseline will be associated with greater initial disease severity.

**Research question 3:** Do variations in disease severity predict variations in fatigue severity over time?

**Hypothesis 3.1** Disease severity as a time-varying covariate will predict changes in fatigue severity over time.

**Research question 4:** Do patterns of fatigue and disease severity in chronic liver disease patients co-vary together over time?

**Hypothesis 3:** Fatigue and disease patterns will be correlated over time.
CHAPTER THREE

Methods

In this descriptive, correlational longitudinal study, patterns of fatigue and liver disease severity were examined in a secondary analysis of data collected on patients enrolled in a clinical trial for liver disease. Gender and baseline symptoms were predictor variables and fatigue and liver disease severity were dependent variables measured longitudinally. Linear mixed-effects models (LMM’s) and multivariate linear mixed-effects models (MLMM’s) were used to examine change in fatigue and disease over time and the correlation between these changes.

Sample and Variables

The original study was that of a randomized, placebo-controlled trial of a bile acid, ursodeoxycholic acid (UDCA), in the treatment of patients with primary sclerosing cholangitis (PSC). One-hundred-fifty patients were enrolled in the original trial from July 2002 to December of 2005. Patients in the study were seen yearly for physical examination, blood tests, and completion of quality of life and fatigue questionnaires. Patients were eligible to participate in the original trial if they met inclusion criteria for a diagnosis of PSC. Inclusion criteria included: 1) chronic cholestatic disease of at least six months’ duration; 2) serum alkaline phosphatase at least 1 ½ times the upper limits of normal; 3) cholangiography demonstrating intrahepatic and/or extrahepatic biliary duct obstruction, beading or narrowing
consistent with PSC; 4) liver biopsy in the previous one year which was available for review and compatible with the diagnosis of PSC

**Exclusion criteria included:** 1) coexistent conditions such as pre-existing advanced malignancies or severe cardiopulmonary disease which would limit their life expectancy to less than two years; 2) inability to provide consent; 3) treatment for their liver disease with medications in the three months prior to study entry; 4) inflammatory bowel disease patients requiring specific treatment in the preceding three months except for maintenance therapy with a 5-ASA compound; 5) anticipated need for liver transplantation within two years (expected survival of <80% at two years based on Mayo risk score); 6) recurrent variceal bleeds, spontaneous uncontrolled encephalopathy, INR > 1.5 uncorrected by vitamin K or resistant ascites that suggested an anticipated survival of less than one year; 7) pregnancy or lactation (patients who became pregnant during the study were discontinued and referred to their physicians); 8) age less than 18 years or greater than 75 years; 9) findings highly suggestive of liver disease of other etiology.

The primary endpoint was time to first failure (death, meeting minimal listing criteria for transplant, development of varices, cholangiocarcinoma or progression to cirrhosis) and was assessed using a Cox model. The study was conducted at Mayo Clinic Rochester, Minnesota and was funded by the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK). The study was a multi-center trial with Mayo Rochester as the Data Coordinating Center (DCC) overseeing six other sites including Mayo Clinic-Jacksonville (Florida), Mayo Clinic-Scottsdale (Arizona), Virginia Mason
Participants enrolled in the original trial had between 3 and 7 years of follow-up at the time of this research. All participants were followed in the trial until they met an endpoint of liver transplantation or death, or if they withdrew from the study and no further contact was possible. Of the original study group, 8 patients died from liver disease, 16 underwent liver transplantation, and 21 voluntarily withdrew from the study. After a planned analysis to be done once 75% of expected endpoints had been reached, the Data Safety and Monitoring Board reviewed the data and terminated the study due to futility. The treatment UDCA was associated with slightly worse clinical outcomes than the placebo (Lindor et al., 2009). Treatment assignment was included as a covariate to determine whether it was associated with a negative effect on the outcomes.

**Study Design**

The study design was that of a descriptive, correlational, longitudinal design examining predictors of fatigue and disease and the correlation between these longitudinal dependent variables. Both fatigue and disease were modeled jointly by use of bivariate longitudinal models to determine whether there were correlations among rates of change. These models examined whether the baseline intercept for fatigue was related to the baseline intercept for disease severity and whether the magnitude of change for fatigue was related to the magnitude of change for disease. Yearly fatigue scores from the FIS and Mayo PSC risk scores collected as part of the original study
were used as the dependent variables. Those patients with a minimum of one fatigue assessment were included in this study.

Measures

Fatigue measurement

The fatigue instrument used in the original trial and which was used in this study was the Fisk Fatigue Impact Scale (FIS) which is a 40-item, 4-point Likert-type scale survey with 4 subscales and a total possible score of 160 (Fisk et al., 1994). The FIS was constructed with the viewpoint that measuring the effect of fatigue on activities is more sensitive than simply asking patients to rate fatigue. As stated by Monks (1989), “symptoms should be considered in terms of the patient’s own expected activity levels and relationships and compared with those situations in which these expectations are not met”. The FIS was therefore constructed to capture patients’ perceptions of the functional limitations that they attributed to their symptoms of fatigue. A period of the past month was used for the scale to provide a measure that could be used to study changes in patients’ perceptions over time while allowing for a reasonable period in which judgments about the impact of fatigue could be made (Fisk et al.). The FIS was constructed to include three subscales to assess the perceived fatigue impact on cognitive functioning (10 items), physical functioning (10 items) and psychosocial functioning (20 items). The FIS asks respondents to rate how much of a problem fatigue has caused them in reference to statements such as “Because of my fatigue I have difficulty paying attention for a long period” or “Because of my fatigue I have to be careful about pacing my physical activities”, etc. The subject is asked to circle the
appropriate response for each: 0 = no problem; 1 = small problem; 2 = moderate problem; 3 = big problem; 4 = extreme problem.

The FIS has undergone evaluation in liver disease populations with good evidence of construct-related validity, and internal and test-retest reliability (Prince, James, Holland, & Jones, 2002). The correlation between the assessment of fatigue measured by the FIS and the visual analogue scale was strong ($r = .73$, $p < .001$). Test-retest reliability was computed with a coefficient of reproducibility at 13% of the mean, which was notably better than the variability of the VAS at 33%. The coefficient of reliability is calculated as described by Bland and Altman (1983). This method differs from the correlation coefficient which is a measure of association, rather than agreement. The method examines the differences between the results of the repeated tests and assumes that the differences between the measurements arise from random variation and are therefore normally distributed, whether or not the actual measurements are normally distributed. The coefficient of reliability is calculated as twice the standard deviation of these differences (equivalent to the 95% confidence limit of these differences). Dividing this by the mean value gives the proportion by which the mean value could vary due to imperfect reproducibility in 95% of the cases. Internal reliability of the FIS total score was found to be excellent with Cronbach’s $\alpha = .98$ for the total score and subscales yielding Cronbach’s $\alpha > .87$ in a group of multiple sclerosis, hypertension, and chronic fatigue patients (Fisk et al.). The FIS has been shown to be reproducible both at short and long intervals indicating its reliability in assessing fatigue (Prince, James, Holland, & Jones). Median FIS scores were found to
be 2.3 times higher in patients with PBC than in chronic disease controls, with a similar
degree of fatigue also found in PSC patients (Kumar & Tandon, 2002). A Cronbach’s
alpha was calculated on baseline values in the sample for this research (n = 116) and
was 0.94.

Liver disease severity

The Mayo risk score is a natural history model based on the variables of age,
bilirubin, aspartate aminotransferase (AST), variceal bleeding and albumin. The model
was developed from a multivariate analysis of 405 patients with primary sclerosing
cholangitis from 5 clinical centers (Kim et al., 2000). The risk score for patients with
PSC is defined by the following formula: 
\[ R = 0.03 \text{ (age [y])} + 0.54 \log_e (\text{bilirubin [mg/dl]}) + 0.54 \log_e (\text{aspartate aminotransferase [U/L]}) + 1.24 (\text{variceal bleeding [0/1]} – 0.84 (\text{albumin [g/dl]}). \]
For the variable of variceal bleeding a score of 0 is used for
patients without a history of variceal bleeding, and 1 is used for those with a previous
history of variceal hemorrhage. A history of variceal bleeding was recorded on data
collection forms for the original study at the time of patient visits and refers to evidence
of bleeding from varices or dilated blood vessels in the esophagus. Variceal bleeding is
indicative of increased pressure in the collateral blood vessels due to cirrhotic liver
disease. This risk score is used to estimate survival up to 4 years in patients with
cholestatic liver disease (Kim et al.).

Several scenarios are depicted to provide a better understanding of what
representative scores indicate. As is represented in Table 1, a 43 year old patient with
normal albumin and bilirubin, mildly elevated AST and no history of variceal bleeding
has a 93% estimated survival probability at 4 years. The second and third patients have worse clinical parameters with an 84% and 58% 4-year survival. The fourth example patient has the same parameters as the third with a history of variceal bleeding and a resulting risk score of 3.494 indicating a poor survival probability.

**Symptoms**

Symptom data were collected yearly on study participants as part of the liver disease symptom domain of a disease-specific quality of life instrument. The Quality of Life Survey for Cholestatic Liver Disease (Chol-QOL), formerly termed the NIDDK-QA, assesses the patient reported impact of liver disease on quality of life (Gross et al., 1999). The questionnaire contains 47 questions divided into 4 domains: liver disease symptoms, physical functioning, health satisfaction, and well-being. The Chol-QOL has undergone psychometric evaluation in PSC patients with test-retest reliability at .82 to .99 and internal consistency reliability at .87 to .94 (Kim et al., 2000). The liver disease symptom domain includes questions regarding symptoms and the degree to which patients are bothered by them graded on an “extremely” (4) to “not at all” (0) Likert scale. This liver disease symptom domain contains 18 symptoms some of which reflect side effects of anti-rejection medications used in patients who have undergone liver transplant and would not be appropriate for non-transplanted patients. The symptoms of itching, insomnia, and difficulty with concentration were chosen as there is evidence from the literature they may influence levels of fatigue. As the 4-point Likert scale could be interpreted as ordinal rather than interval level data the responses were transformed. For the purpose of this research, a response to these symptoms of “not at
all” or “a little bit” was coded as if it were not present or 0; a response of “moderately”, “quite a bit” or “extremely” was coded as if it were present or 1.

Data

Data from the original study were collected on data collection forms at the sites, forwarded to Mayo Clinic Rochester and entered into SAS 9.0 (Cary Institute) by data entry personnel in the Data Coordinating Center (DCC). Periodic data clean-up was done with frequencies and queries done to determine missing values and duplicate entries addressed throughout the study. Any queries were answered by examining the original data collection forms and referring to the patient medical history if needed. The data for this secondary analysis were received from the DCC in Excel format.

The number of actual values on each occasion and patients with one or more fatigue assessments to be included in the analysis was determined. Of the 150 participants who were enrolled in the original study, 135 patients completed the FIS instrument one or more times. One patient completed it at 7 time points, twelve completed it at 6 time points, 17 completed it at 5 time points, 25 completed it at 4 time points, and 28 completed it at 3 time points, 23 completed it at 2 time points, and 29 completed it once. The time points at which the FIS was completed varied. Mayo risk scores were calculated at entry and at all follow-up yearly evaluations. Risk scores were available where there were missing FIS assessments as the risk score could be calculated from data obtained during the visit. There were occasions when the FIS instrument was inadvertently not administered during the patient visit, or the patient did not return the completed FIS instrument. There were 3 completed FIS instruments at
year 6 and 2 at year 7; therefore the number of visits used for the analysis was limited to 5 years of follow-up or 6 time points.

**Data Analysis**

The statistical analyses were performed using SAS version 9.0 (Cary Institute) and SPSS software version 14.0. The first analyses were to explore the data and to determine the general change of fatigue and disease and the effect of covariates. Descriptive statistics and frequencies of the demographic characteristics and variables to be included in this analysis were performed. Descriptive statistics were computed to compare the group of participants who completed fatigue assessments at one or more times with the remaining patients in the original study to determine whether the sample was different in any significant way.

The second part of the analysis was done to fit univariate and bivariate linear mixed effect models to the data to explore the change in fatigue and disease severity and test the effects of gender and baseline symptoms. Longitudinal models are useful for answering questions about change including how to characterize individual patterns of change over time and the association between certain predictors and these patterns of change (Singer & Willett, 2003). Linear mixed effect models allow analysis of longitudinal data where the mean response is modeled as a combination of population characteristics and subject-specific effects unique to individual persons (Fitzmaurice, Laird & Ware, 2004). The former are called *fixed effects* and the latter are *random effects*; the term *mixed* designates a model that includes both. These models also are
Flexible in accommodating any degree of imbalance in longitudinal data including missing data and measurements taken at different time points (Fitzmaurice et al.).

**Analysis for Aim 1**

Aim 1 was to describe the patterns of fatigue and disease severity in chronic liver disease patients over a period of up to 5 years. Spaghetti plots of the FIS measures and Mayo risk scores were examined to determine the variability and trend in fatigue and disease trajectories. Individual trellis plots were graphed on a subset of the participants to determine individual patient patterns of fatigue and disease. Correlational matrices were calculated to determine the pattern of correlation over time for both the FIS and Mayo risk scores. Means and standard deviations were calculated for fatigue and risk scores at all 6 time points. Linear mixed effects models were used to describe the pattern of individual person fatigue and disease patterns and the effect of predictors. At the level-1 model, time was used as the predictor variable for predicting initial patient fatigue and disease levels and describing within-individual change in fatigue and disease outcomes.

Within-individual changes in fatigue and disease severity were examined by use of unconditional mean and growth models. Time referred to the length of time of follow up which was from baseline to 5 years or up to 6 yearly assessments. Three level-1 models were compared including a) no change over time, (b) change at a constant rate or linear, and (c) change that does not occur at a constant rate or quadratic. In the level-1 model, time or visit in years is considered the independent variable for predicting
initial levels of fatigue and disease severity and trajectories. At this point the model was constrained to be unconditional or with no predictors.

In the level-1 model the unit of analysis is the person-year. This level consists of repeated observations of individuals over time. In a model of linear change, the outcome variable or $Y$ (fatigue or disease) is represented as a function of time where $\beta_{0i}$ is the intercept for individual $i$, $\beta_{1i}$ is the linear slope for individual $i$, $\beta_{2i}$ is the quadratic slope for individual $i$, and $e_{ij}$ is the residual for individual $i$ at occasion $t$:

$$Y_{it} = \beta_{0i} + \beta_{1i} \text{Time}_{it} + \beta_{2i} \text{Time}^2_{it} + e_{it}.$$  

Time as measured in years from initial study visit. The error represented as $e_{it}$ is assumed to be normally distributed with a mean of 0 and constant variance $\sigma^2$.

The first research question addressed the general pattern of fatigue and disease trajectories in patients. It was hypothesized that the shape would be linear or quadratic.

Model Selection for the Covariance Structure

The models for fatigue and risk score were compared to determine the best covariance structure using a method called restricted maximum likelihood estimation (REML). This is a form of maximum likelihood (ML) estimation which is a method used to fit linear mixed effect models to data that maximizes the likelihood of observing obtained parameter estimates for a particular study sample. REML is used when comparing variance components of the model as this method takes into account the fixed effects and is therefore less biased than ML. Each covariance structure was fit to the data and the models ranked according to Akaike information criterion (AIC) and Bayes information criterion (BIC) which are goodness of fit statistics used as
covariance model selection criteria. These selection approaches compare adjusted log
likelihoods for a model \((m)\) penalized for the number of parameters represented by \(q\) for
AIC and \(\log(N)\) for BIC in the covariance model (Weiss, 2005). The model with
smallest value of AIC or BIC was selected as the best structure.

AIC and BIC for a model are defined as:

\[
AIC(m) = -2 \log \text{likelihood}(m) + 2q_m
\]

\[
BIC(m) = -2 \log \text{likelihood}(m) + \log(N)q_m
\]

The goodness of fit statistics computed using the two methods refer to different portions
of the model. Under ML they describe the fit of the entire model where with REML
they describe only the random effects or variance components of the model. This means
that the goodness of fit statistics from ML can be used to test hypotheses about any type
of parameter where those with REML can only be used to test variance components
(Singer & Willett, 2003). The REML method is most correct when comparing models
that differ in random effects or covariance parameters only and was used to determine
the best covariance structure for the models in this research.

**Analysis for Aim 2**

Aim 2 was to determine the predictive effect of gender and baseline symptoms
on fatigue and disease trajectories in chronic liver disease patients over a 5-year period.

Linear mixed models were used to capture variations in initial fatigue and
disease severity, and changes in fatigue and disease over time. Covariates including
gender, co-existent symptoms, and disease duration were studied to see whether these
variables were associated with fatigue and disease trajectories. For this analysis male gender was coded as “0” and female as “1”.

The level-2 models allow the determination of the extent that baseline and trajectories vary as a function of covariates. In level-2, the person-specific change parameters are outcomes that vary across individuals. The intercept and slope are random variables with variation across individuals. These outcomes are modeled as a function of demographic and disease related characteristics that vary between individuals, plus error associated with the individual. The second level coefficients describe how variations in baseline characteristics of the individuals or the level-2 parameters can explain differences in the intercepts ($\beta_{0i}$ = initial fatigue or disease level) and slopes ($\beta_{1i}$ = linear fatigue or disease trajectory coefficients; $\beta_{2i}$ = quadratic fatigue or disease trajectory)

\[
\begin{align*}
\beta_{0i} &= \gamma_{00} + \gamma_{01}\text{Gender} + \gamma_{02}\text{Symptoms} + \gamma_{03}\text{DiseaseDuration} + u_{0i} \\
\beta_{1i} &= \gamma_{10} + \gamma_{11}\text{Gender} + \gamma_{12}\text{Symptoms} + \gamma_{13}\text{DiseaseDuration} + u_{1i} \\
\beta_{2i} &= \gamma_{20} + \gamma_{21}\text{Gender} + \gamma_{22}\text{Symptoms} + \gamma_{23}\text{DiseaseDuration} + u_{2i}
\end{align*}
\]

This stage of the analysis examined inter-individual differences in the trajectories of fatigue and disease by modeling the individual change parameters (intercept and slope) as a function of proposed predictors at Level 2.

The combined model with level-2 predictors is as follows:

\[
Y_{it} = \gamma_{00} + \gamma_{01}\text{Gender} + \gamma_{02}\text{Symptoms} + \gamma_{03}\text{DiseaseDuration} \\
+ \gamma_{10}\text{Time} + \gamma_{11}\text{Gender} + \gamma_{12}\text{Symptoms} + \gamma_{13}\text{DiseaseDuration} \\
+ \gamma_{20}\text{Time}^2 + \gamma_{21}\text{Gender} + \gamma_{22}\text{Symptoms} + \gamma_{23}\text{DiseaseDuration} \\
+ u_{0i} + u_{1i} + u_{2i}
\]

43
Predictors tested in the model included gender, disease duration at baseline, baseline symptoms of insomnia, concentration difficulty and itching which were all time-invariant.

To examine whether the predictors of interest (gender, co-existent symptoms and disease duration) would explain the patterns of fatigue, the null hypothesis that was tested is that there is no covariate interaction with the intercept or rate of change, or that there are no effects due to the covariates. The effects of the covariates were tested at $\alpha = .10$ level.

**Analysis for Aim 3**

Aim 3 was to determine the predictive effect of disease severity as a time-varying covariate on levels of fatigue. Risk score values were allowed to vary over time. As risk score varied randomly it was considered a *stochastic* time varying covariate. In addition risk score was considered an *external* time varying covariate, which means that future values are not predicted by the outcome fatigue. The values of an external time varying covariate are considered impervious to issues of reciprocal causation. As a result of these assumptions, model parameters could be given a causal interpretation (Fitzmaurice, Laird & Ware, 2004). Changes in the time-varying predictor fixed effects and associated fit statistics were considered in deciding whether to retain them in the model.

An individual’s level of fatigue $Y$ at time $t$ depends on the number of years in the study (time) and the contemporaneous value of risk score (disease) and three person-specific residuals.
A composite specification for a model including disease severity as a time-varying covariate is depicted below.

\[ Y_{it} = \gamma_{00} + \gamma_{01} \text{Gender} + \gamma_{02} \text{Symptoms} + \gamma_{03} \text{DiseaseDuration} + \gamma_{04} \text{RiskScore}_{ij} + \gamma_{10} \text{Time}_{ij} + \gamma_{11} \text{Gender} + \gamma_{12} \text{Symptoms} + \gamma_{13} \text{DiseaseDuration} + \gamma_{14} \text{RiskScore}_{ij} + \gamma_{20} \text{Time}^2_{ij} + \gamma_{21} \text{Gender} + \gamma_{22} \text{Symptoms} + \gamma_{23} \text{DiseaseDuration} + \gamma_{24} \text{RiskScore}_{ij} + u_{0i} + u_{1i} + u_{2i}. \]

**Analysis for Aim 4**

Aim 4 was to determine the co-variation of fatigue and disease severity over time or how the two trajectories interrelate. The question as to whether change appears similar across fatigue and disease was examined. In addition the effect of gender and symptoms across these outcomes were measured. These two variables were treated as a bivariate response measured repeatedly over time. These models can be used to identify the type and nature of the correlations across responses. When the two response variables are measured at the same time point, but one response has missing data when the other is observed, the bivariate model may improve the precision of the effect estimate (Weiss, 2005). Tests of specific effects for a single dependent variable are more powerful in a multivariate analysis and will be apparent in the form of smaller standard errors (Snijders & Bosker, 1999).

Multivariate linear models are similar to univariate models with the exception that the multiple response variables can be modeled jointly. They can allow for the examination of differential effects of predictors across outcomes. They have many advantages over treatment of one of the response variables as a time-varying predictor.
It may not be clear as to which response is better suited to being the response or predictor and both response variables need to be measured at that time point for the other to be included (Weiss, 2005) Multivariate random effect models allow for estimates of residual variances for each outcome as well as estimates of variances and covariances for random change parameters both within and between outcome variables (MacCallum, Kim, Malarkey & Kiecolt-Glaser, 1997).

In specifying a multivariate multilevel model, the data are treated as if only a single outcome variable is measured. Operationally the two outcome measures on a given individual are stacked to form a single vector which is then treated as a single variable. Let $Y_{itk}$ be the response for individual $i$ at occasion $t$ on outcome $k$. The conventional univariate random effects model can be extended to the multivariate case by the introduction of dummy variables to indicate each dependent variable $\delta_1, \delta_2, \ldots, \delta_p$. If a given measure is on $Y_k$, $\delta_k = 1$ and $\delta_k = 0$, if otherwise. The model for linear change borrowed from MacCallum et al. (1997), could be extended as follows:

\[ Y_{itk} = \sum \delta_k (\gamma_{0ik} + \gamma_{1ik} \text{Time}_{itk} + e_{itk}) \]

where $\gamma_{0ik}$ is the intercept for individual $i$ on outcome $k$, and $\gamma_{1ik}$ is the slope for individual $i$ on outcome $k$, $\text{Time}_{itk}$ is the measure of time for individual $i$ on occasion $t$ for outcome $k$, and $e_{itk}$ is the residual for individual $i$ at occasion $t$ for outcome $k$. Below $\gamma_{0k}$ and $\gamma_{1k}$ depict the fixed effects for the intercept and slope on outcome $k$, $u_{0ik}$ and $u_{1ik}$ represent the random variation of individuals around the mean intercept and slope, respectively for outcome $k$. 

46
The intercepts and slopes for the outcome variables are themselves random variables with variation across individuals modeled as follows:

\( \gamma_{0ik} = \gamma_0 + u_{0ik} \)  
\( \gamma_{1ik} = \gamma_1 + u_{1ik} \)

Substitution of equations 6 and 7 into equation 5 yields a combined multivariate model:

\[
Y_{itk} = \sum \delta_k (\gamma_{0k} + \gamma_{1k} \text{Time}_{itk} + u_{0ik} + u_{1ik} \text{Time}_{itk} + e_{itk})
= \sum (\gamma_{0k} \delta_k + \gamma_{1k} \delta_k \text{Time}_{itk} + \delta_k u_{0ik} + u_{1ik} \delta_k \text{Time}_{itk} + \delta_k e_{itk})
\]

The fixed intercept terms for the \( k \) response variable are regression coefficients for the dummy variables and the fixed slope terms are regression coefficients for product variables of one dummy variable and the time measure. The estimation yields estimates of a fixed intercept \( \gamma_{0k} \) and a fixed slope \( \gamma_{1k} \) for each outcome \( k \).

Random effects are estimated for each outcome variable: intercept variance \( (\sigma^2_{u0k} = var(u_{0ik})) \); residual variance \( (\sigma^2_{ek} = var(e_{itk})) \); slope variance \( (\sigma^2_{u1k} = var(u_{1ik})) \); and covariance of intercepts and slopes \( (\sigma_{u01k} = cov(u_{0ik}, u_{1ik})) \). Random effects can also be estimated for covariances of intercepts and slopes for each pair of outcomes \( j \) and \( k \):

\( \sigma_{u0j1k} = cov(u_{0ij}, u_{1ik}) \), the covariance of intercepts on outcome \( j \) with slopes on outcome \( k \); \( \sigma_{u0j0k} = cov(u_{0ij}, u_{0ik}) \), the covariance of intercepts on outcome \( j \) with intercept on outcome \( k \); and \( \sigma_{u1j1k} = cov(u_{1ij}, u_{1ik}) \) the covariance of slopes on outcome \( j \) with outcome \( k \). The process of fitting the multivariate model produces covariance matrices for between-person variance components (random intercepts and random slopes) and for within-person variance components (Sliwinski, Hall, & Hofer, 2003).
**Missing Data**

Although the maximum duration of follow-up for patients enrolled early in the study is 7 years with 8 observations, patients enrolled at the end of the study had a maximum of 5 years of follow-up or 6 observations each. Patients dropped out of the study voluntarily, were non-compliant, underwent liver transplant, or died, resulting in unbalanced data. If study personnel did not administer the fatigue questionnaire, or a patient did not complete it during the visit, missed assessments resulted. Risk score data were fairly complete as these scores could be calculated from visit data or mailed in blood tests and did not require study personnel to administer or patients’ time to complete.

Incomplete data can result in loss in the precision with which the mean response can be predicted over time (Fitzmaurice et al., 2004). Parameter estimates may be biased and generalizations incorrect; however, it is not the “missingness” of the data itself that is the problem but rather the reasons data are missing (Singer & Willett, 2003). There are two types of missing data mechanisms to accommodate the reasons for incomplete data. Data are missing completely at random (MCAR) when the missingness in the outcome is simply the result of a chance mechanism that does not depend on either observed or unobserved components of the outcome \( Y \). An assumption that data are MCAR is considered to be generally implausible and impossible to verify (Raudenbush, 2001). The MCAR assumption may be most tenable for those patients who missed an occasional fatigue assessment but did not drop out of the study completely as it is unlikely this occurred for reasons other than due to chance. As
MCAR is difficult to prove, the mechanism for occasional missed fatigue assessments is more likely MAR. In contrast to MCAR, data are said to missing at random (MAR) when the probability that responses are missing depends on the set of observed responses but is unrelated to the missing values that ideally would have been obtained (Singer & Willett).

If the cause of the missing data is neither MCAR nor MAR, the mechanism for missing data would be that they are not missing at random or NMAR. Missing data are said to be NMAR when the probability that responses are missing is related to the specific values that should have been obtained (Fitzmaurice, Laird & Ware, 2004). This NMAR mechanism is also nonignorable missingness. In this situation the cause of a subject’s dropout depends on their unobserved or post dropout responses even in the context of the observed data. This is a possible mechanism for risk scores in patients who dropped out of the study due to liver transplant or death. Subjects do not have risk scores or fatigue scores at a time when these outcomes are likely to be quite different. It is not possible to test whether data are MAR rather than NMAR as the data that would allow this assumption to be tested are missing (Fairclough, Thijs, Huang, Finnern, & Wu, 2008).

Some patients dropped out of the study for voluntary reasons, others were transplanted or died. A test for the missing data mechanism of these incomplete longitudinal data as proposed by Park and Lee (1997) was used to determine whether the missing observations in dropouts were MCAR or MAR. An indicator variable was defined for those patients who dropped out of the study and an extended model
including the indicator variable and the covariates for the fatigue assessments were fit to the data. This was also done in an extended model for risk scores. The regression coefficients associated with the indicator variables were tested as interactions to see whether they were significantly different from zero, in which case the missing data mechanism would not be MCAR and would be assumed to be either MAR or NMAR.
CHAPTER FOUR

Results of Analysis

The purpose of this chapter is to describe characteristics of the study sample and the results of the hypotheses testing. The first is a descriptive analysis which was used to describe the sample and to make comparisons with those patients from the original study, that were not included due to inadequate number of fatigue assessments. This analysis was done to see whether there were any significant differences between the groups.

Sample Characteristics

Of the 150 participants in the trial, 135 completed at least one FIS instrument and constituted the sample in the current study. There were 15 participants who did not complete the fatigue scale at any time point. A comparison of these 135 patients and the remaining study participants is depicted in Table 2. Patients did not differ in age, gender or Mayo risk score. Although Mayo risk score was slightly greater in those patients who did not complete the required number of FIS assessments and were not included in this study, the difference was not significant. The male to female ratio was the same in both groups and represents the larger male predilection in this liver disease. Patients in the study were primarily non-Hispanic and Caucasian. African Americans constituted a lower percent of the 135 patients in this study compared with the group of remaining 15 patients. No differences existed between groups in percent of Hispanic patients.
Of the 135 participants in this study, 116 patients completed the FIS at entry, 84 patients at year 1, 77 at year 2, 67 patients at year 3, 43 patients at year 4, 31 patients at year 5, 3 patients at year 6, and 2 patients at year 7. The duration of follow-up for the purposes of this analysis will be limited to year 5 as the number of patients who completed fatigue assessments at years 6 and 7, was 3 and 2 respectively, a number considered too small to be included in the analyses.

As the statistical analysis should always be preceded with a graphical display of the data (Fitzmaurice, Laird & Ware, 2004), the data were plotted with use of individual spaghetti plots which are scatter plots with the points connected by lines. The method of focusing on these plots can be used in longitudinal data when the design is balanced with the timing of the repeated measures common to all individuals but can also handle data that are incomplete but balanced (Fitzmaurice, Laird & Ware). Plots were examined to determine trends and the general shape. Plots of fatigue and risk score are depicted in Figure 1 and Figure 2. There is a high degree of variability in intercepts for fatigue but not clear indication of rising levels throughout the sample. There is evidence of variability of the general shape of the slopes for fatigue and disease in that linear and quadratic time effects should be tested.

Trellis graphs of fatigue and risk score levels over time on a subset of patients are depicted in Figure 3 and Figure 4. It is not clear that there is any relationship between the levels of the intercept for both outcomes or between the slopes for both outcomes in individual people.
Means and standard deviations and correlation matrices were calculated for both outcome variables (Table 3 and Table 4). The standard deviations show the least variability in scores at baseline with increasing variability over time, with decreasing numbers of patients measured. Correlations remain stable with little or no decrease with increasing time intervals.

Mayo risk scores were calculated yearly on patients and there were more assessments of risk score than fatigue measurements. This was due to the fact that some patients did not complete them, where risk scores would be calculated on any patients who had a yearly evaluation and blood tests (Table 4). The mean risk score for patients gradually increased over time, partly due to the fact that age is included in the model for calculating risk score but also due to disease progression. The correlation between measurements decreased with increasing time separation.

Covariance Structure

As one of the defining features of longitudinal data is their correlation, it is important to appropriately model the covariance to ensure that correct standard errors are obtained and valid inferences about the regression parameters can be made (Fitzmaurice, Laird & Ware, 2004). Because model selection criteria for the mean response depend upon the correct specification of the model for the covariance the first step was to choose an appropriate model for the covariance. This model for the covariance depends on the assumed model for the mean as the model for the covariance accounts for the covariance among the residuals, which result from a specific model for the mean. This model can include the main effects of time and all other main effects and
interactions. The choice of a model for the covariance was based on a “maximal model” for the mean, to minimize any misspecification of the model for the mean. Once this model had been chosen, the residual variation and covariance were used to determine a suitable model for the covariance.

Several alternative covariance structures were tested that appeared appropriate for the data and are widely used in longitudinal data analysis (Singer & Willett, 2003). These include unstructured, compound symmetry, and autoregressive. These covariance structures were fit using restricted maximum likelihood (REML) as the estimates from this method only reflect the stochastic portion, which is the general purpose of this part of the analysis. These models were fit to the fatigue data (Table 7) and risk score data (Table 8) separately. From a review of the results a random effects structure with unstructured covariance pattern was selected for all subsequent models for both fatigue and disease outcomes.

**Research Question 1**

The first research question addressed the pattern of change in the fatigue trajectory over time and whether it was linear or quadratic. It is recommended that an unconditional means model be fitted first (Singer & Willett, 2003). An unconditional means model includes no predictors at either level and simply describes and partitions the outcome variation.

\[
Y_{ij} = \gamma_{00} + e_{ij}
\]

\[
\gamma_{00} = \beta_0 + u_{0i}
\]
This model stipulates that at level 1, the true individual change trajectory for person \( i \) is completely flat at level \( \beta_{0i} \). The model says that although the change trajectories may differ in elevation their average elevation across the population is \( \gamma_{00} \). The true mean of \( Y \) for individual \( i \) is \( \beta_{0i} \), where the true mean of \( Y \) across all people is \( \gamma_{00} \). Rejection of its associated null hypothesis \( (p < .001) \) is evidence that the average fatigue level of patients is not zero.

Linear mixed effect model analyses use three criteria for comparing model fit. These include the -2 log-likelihood (-2LL), the Akaike Information Criterion (AIC), and the Bayesian Information Criterion (BIC). The -2LL is called a deviance statistic and is used for comparing nested models. The deviance is regarded as a measure of lack of fit between model and data, but its typical use is in examining differences in deviance values for models fitted to the same data. The deviance statistic is compared to a \( \chi^2 \) distribution with degrees of freedom equal to the difference in the number of model parameters between two models. The AIC and BIC criteria can also be used to compare the relative fit of two models fit to an identical set of data. The AIC criterion penalizes for the estimation of each additional covariance parameter between models and the BIC penalizes for both additional parameters and sample size. These criteria are used to compare the goodness-of-fit of alternative models that are not nested. The AIC can be used to compare models with the same fixed effects parameters, but different models for the covariance. As the BIC extracts a very large penalty for each additional covariance parameter, it risks selection of a model that is too parsimonious for the data and is
generally not recommended (Fitzmaurice, Laird & Ware, 2004). Better model fit is indicated by smaller values of AIC and BIC. Methods for this statistical estimation include maximum likelihood (ML), which maximizes the likelihood of sample data, and restricted maximum likelihood (REML), which maximizes the log likelihood of the sample residuals. The two methods differ little with respect to estimating regression coefficients but do differ in estimation of variance components, a difference most important in a small sample (less than 30) but immaterial in larger sample sizes (Snijders & Bosker, 1999).

**Unconditional means model for fatigue**

The unconditional means model for fatigue in Table 5 provides a baseline assessment by which to compare more complex models. The model for fatigue will be described first. As there is only one fixed effect in this model, the intercept, the estimate of 29.16 ($p < .001$) is the average fatigue level over time in this group of patients, indicating that patients have a non-zero level of fatigue. There is statistically significant variance within-persons (197.06, $p < .001$) indicating that fatigue scores in individual patients vary from time point to time point. There is also statistically significant variance between-persons (777.02, $p < .001$) indicating that fatigue levels differ between patients. The addition of a linear term approaches statistical significance (1.05, $p < .10$). Statistically significant variability between persons in initial status and slopes indicate people differ substantially from these averages ($\sigma_0^2 = 712.63$, $p < .001$; $\sigma_1^2 = 6.38$, $p < .05$). A test of the set of differences between the no change and linear models by the difference in deviance statistics (-2log likelihood) was (12.7) which exceeded the
0.05 critical value of a \( \chi^2 \) distribution \((d.f. = 3)\). The linear term was retained in the model as its fixed effect approached statistical significance and is needed to describe the temporal pattern.

A quadratic term was then added as a fixed effect to the model, but was not significant so was not retained. In addition the AIC and BIC values were larger in the quadratic model. The random intercept and slope linear model was selected.

**Unconditional means model for risk score**

The unconditional means model for risk score in Table 6 has an intercept of 0.383 which is the average risk score for patients across time. Statistically significant variance is found both within \((0.260, p < .001)\) and between persons \((0.665, p < .01)\) suggesting that people differ significantly from this average. Linear fixed and random effects added to the model were significant \((0.096, p < .001; 0.026, p < .001)\), indicating that patients have a non-zero rate of increase in their disease severity but also vary significantly from that rate. A comparison of deviance statistics between the no change and linear models was statistically significant as the deviance declined by 138, far greater than the associated .05 critical value of 18.5 \((d.f. = 3)\)

Quadratic fixed and random effects \((\text{time}^2)\) were significant \((0.029, p < .001; 0.002, p < .05)\). The linear term is negative and non-significant, but retained in the model. Disease severity in patients worsens at a non-linear and accelerated rate. A comparison of deviance statistics between the linear and quadratic model was 22.5, which is greater than the .05 critical value of 9.49 \((d.f. = 4)\). These results in addition to the smaller AIC and BIC values provide evidence for adoption of the quadratic model.
A higher-level polynomial was attempted but unsuccessful due to problems with convergence. In answer to the first research question, the structural form for the level-1 individual growth models, a linear model was selected for fatigue and quadratic model for risk score.

For risk score (Table 6) the estimated within-person variance is 0.260 and the average between-person variance is 0.665. This unconditional means model allows for a calculation of the intraclass correlation coefficient or ICC, which describes the proportion of total variance that lies between people. The ICC is the between-persons variance divided by the between persons-variance plus the within-persons variance. For fatigue levels it is $777.02/777.02+197.06$ or .798 or 80% indicating that a large majority of the variance in fatigue lies between patients rather than within. For risk score, the ICC is $0.665/0.665+0.260$ or 0.723 or 72% indicating that most of the variance in risk scores is between patients rather than within. For both dependent variables the majority of the total variation in scores lies between individual people. The ICC provides information on the size of the residual autocorrelation in the unconditional means model. It quantifies the magnitude of composite residuals across occasions for individual persons, estimating the average correlation between any pair of composite residuals. An ICC of 0.50 is considered quite large (Singer & Willett, 2003). Those for the fatigue and disease unconditional models are very large and indicate that there are significant differences in both fatigue and disease patterns to be modeled.
Research Question 2

The second research question examined how covariates of gender and co-existent symptoms and disease duration predicted inter-individual change in patient fatigue and disease trajectories. Separate linear mixed effects models were fitted to fatigue and disease trajectories. Time-fixed covariates of gender, symptoms of insomnia, concentration difficulty and itching, and disease duration in years were used in both models. Interactions tested between gender, co-existent symptoms and time (visit) were not significant and not included in the univariate models for fatigue and disease. Gender was modeled as 0 = male and 1 = female. Symptoms of insomnia, concentration and itching were coded 0 for responses of “not at all” or “a little bit”, and as 1 for responses of “moderately”, “quite a bit”, or “extremely”. Disease duration at baseline was in number of years since initial diagnosis of liver disease. As the data came from a treatment trial evaluating UDCA versus placebo, treatment assignment was included and coded as “0” for placebo and “1” for UDCA. These covariates were entered as level-2 predictors to examine between persons effects. Linear mixed effect models were fitted using SAS PROC MIXED.

Multilevel model for fatigue change

For the multilevel model for fatigue covariates were introduced into the model. Each covariate was checked for statistical significance one at a time and added to the model based on a cutoff for statistical significance, a variation of the forward selection method described by Weiss (2005). Interactions between gender, visit, and each symptom were also tested for statistical significance. Those reaching a significance
level of $p < .05$ or of theoretical importance were included in the final model. The linear mixed effects model with random slope and intercept for the outcome of fatigue is in Table 9. The average initial fatigue level for male patients without baseline symptoms of insomnia or difficulty with concentration is 13.08 ($p < .001$). With each 1 year of follow-up fatigue increases by 1.04 ($p < .10$) controlling for gender and baseline symptoms of insomnia and concentration. Female patients had on average fatigue levels 10.83 points higher than male patients, controlling for baseline symptoms, a difference that was statistically significant. Most statistically significant was the baseline symptom of difficulty with concentration, which when present was associated with a 25.6 point higher fatigue level than if not present. Itching was not significant when tested in a univariate model.

The estimate for within-person variance $\sigma_e^2$ is 165.26, which is reduced from the unconditional growth model for fatigue. The between-person variance $\sigma_0^2$ was also down to 485.88 from 712.63, indicating an improved fit in estimating initial status. The inclusion of the covariates explained 32% of the variance in initial status (712.63-485.88/712.63 = 0.32. A slight improvement was seen in the fit for fatigue change by the reduced linear slope variance $\sigma_1^2$ from 6.36 to 6.18 indicating the covariates explain 3% of the variance in fatigue change.

**Multilevel model for disease change**

Table 10 describes the results of fitting a linear mixed effect model to the risk score data. Fixed effect estimates indicate the presence of a significant quadratic trend
in risk score change at .030 ($p < .001$), which as positive indicates an accelerated increase in disease severity. Although the linear term suggests that risk score decreases over time, the quadratic term removes more than the linear term adds and causes the trajectory to rise. The presence of itching at baseline was associated with a risk score significantly higher than in those without itching (0.424, $p < .01$). People with insomnia did not differ in risk score levels from those without. Duration of disease at baseline was associated with an increased risk score ($p < .05$).

Comparing the estimates to those from the unconditional model, inclusion of the covariates improved the fit in initial status as seen by the reduction in between-person variance $\sigma_0^2$ from 0.523 to 0.434. The covariates explain 17% of the between-person variance in risk score. The level of within-person variance $\sigma_e^2$ was not improved as seen by the slight increase from the unconditional quadratic model from 0.138 to 0.140. The variance component for the change rate went from 0.052 to 0.044, a reduction of 15%. Variance in the quadratic term $\sigma_2^2$ was unchanged.

**Missing Data Pattern**

In order to determine the nature of the missing data mechanism in the fatigue and risk score data in those patients who dropped out of the study, models were fit with an indicator variable for those who dropped out of the study. This would test whether the intercepts, linear and quadratic effects, in addition to gender and co-existent symptoms, were the same for those with complete follow-up and those who dropped out. If the indicator variable was significant, interactions were tested with covariates.
The indicator variable for the fatigue model was not significant indicating that there were no significant differences in fatigue levels between those with complete data and dropouts. The addition of an indicator variable for dropouts did not change the model parameters.

The indicator variable for the risk score model was significant and indicated that patients who dropped out of the study had a risk score that was 0.60 points higher ($p < .0001$) than those who remained in the study. When interactions with the covariates were tested, only the interaction between the indicator variable and itching was significant, providing evidence that patients with itching who dropped out of the study had a risk score 0.82 points higher ($p < .005$) than those patients without itching who remained in the study.

**Research Question 3**

The effect of risk score as a time-varying covariate was tested and is shown in Table 11. Risk score was added to the model with gender, and symptoms of insomnia and concentration and tested as a main effect. This gave an estimate of 0.368, which was not significant indicating that there is no relationship between varying values of risk score as a predictor for fatigue. The addition of risk score as a time-varying predictor actually resulted in increased level-1 within-person variance from 165.26 to 165.66. The goodness of fit criteria increased indicating that risk score, as a time-varying predictor should not be retained in the model.
Research Question 4

The fourth research question addressed how fatigue and disease trajectories correlate over time. To answer this question a bivariate longitudinal model was used to jointly model how these two dependent variables co-vary over time. As the two dependent outcomes were not on the same measurement scale they were standardized by computing z-scores with a mean of zero and standard deviation of one. This was needed to compare the effects of predictors across these two outcomes. The residual errors for fatigue and disease were allowed to be correlated when observed at the same time occasion. The full model allowed for all random effects to be correlated. A plot of the means of the standardized scores for both outcomes is depicted in Figure 5.

Multilevel model for bivariate linear change

A bivariate random intercept and slope model was fit to the fatigue and risk score data and is shown in Table 12. This resulted in four random effects for each subject, a random intercept and slope for fatigue and a random intercept and slope for risk score. Significant predictors for fatigue and risk score from the univariate models were included in addition to treatment assignment from the original trial. Disease duration in years at baseline was included. Analysis of fixed effects provided evidence of significant increase in both fatigue and disease severity as the linear terms were significant. In comparing the effect of predictors across these outcomes, the effect of time increased disease severity by a greater degree (0.103, \( p < .001 \)) than fatigue severity (0.033, \( p < .10 \)). Significant effects were seen for female gender (0.214), and for concentration difficulty (0.928) on fatigue but not on disease. Baseline fatigue in
women was 0.214 units greater than in men. Concentration difficulty, when controlling for gender, other symptoms, treatment assignment, and disease duration was associated with an almost full standard deviation increase in baseline fatigue. Itching was associated with both significantly greater initial fatigue levels (0.293, \( p < .05 \)) and worse disease severity (0.516, \( p < .001 \)). Greater disease duration was associated with lower fatigue levels, but greater disease severity at baseline.

Table 13 shows the variances, covariances and correlations among the random intercepts and slopes. All variances for intercepts and slopes are significant as seen by noting that each variance is at least several times the magnitude of its approximate standard error. Liver disease patients showed statistically significant variance in their rates of linear change in fatigue and disease. The covariance between fatigue and disease slopes is not significant, indicating that the rates of linear change are not correlated across individuals, even though significant linear trends were found from the estimates of fixed effects. The correlation between the disease intercept and slope is significant (0.328, \( p < .05 \)) implying that PSC patients with worse disease severity at baseline had an accelerated worsening of their disease over time.

**Multilevel model for bivariate linear and quadratic change**

As a quadratic effect was significant for disease severity in the univariate model, it was included along with a linear effect as random effects in a second bivariate model for disease and disease covariates (Table 14). Only the linear effect was used for fatigue and fatigue covariates in this model, as the quadratic effect was not significant for fatigue in the univariate model. Analysis of fixed effects provides evidence of
significant increase over time in fatigue levels ($0.035, p < .05$). The slope for disease severity is no longer linear with the addition of a significant positive quadratic effect indicating an accelerated and nonlinear change in disease ($0.031, p < .001$). Significant effects were again seen for female gender ($0.244, p < .01$) and concentration difficulty on fatigue ($0.965, p < .001$) when controlling for other covariates. Women had a 0.244 standard deviation higher level of baseline fatigue than did men. Those patients with concentration difficulty had a level of baseline fatigue almost a full standard deviation higher than did those without concentration difficulty. Itching was associated with increases in both baseline fatigue ($0.303, p < .05$) and disease severity ($0.496, p < .001$).

Table 15 shows the variances, covariances and correlations among the random intercepts and slopes for fatigue and disease, and the quadratic slope for disease. All variances for intercepts and slopes are significant and have increased with the addition of the quadratic effect for disease. There is a significant and positive correlation between level of baseline fatigue and linear slope for disease ($0.558, p < .05$). The quadratic effect for disease correlated inversely with baseline fatigue. The addition of the random quadratic effect for disease reduced the -2 log REML likelihood 1884.1 to 1855.1 a difference of 29. With four additional parameters, comparison with a chi-square distribution ($d.f. = 4$) results in improved model fit ($p < .0005$).
CHAPTER FIVE

Discussion

This chapter presents a summary and discussion of the study results. It focuses on how the study addressed each aim and provides interpretation of the study findings. Limitations of the study will be acknowledged. The chapter includes implications for future research and practice.

This dissertation was based on a study evaluating the trajectories of fatigue and disease severity in patients with chronic liver disease over a five-year period. A secondary analysis was done of longitudinal data collected as part of a National Institute of Health (NIH) funded randomized, controlled trial evaluating the bile acid ursodeoxycholic acid (UDCA) in patients with primary sclerosing cholangitis (PSC). Self-reported fatigue measured by the Fatigue Impact Scale (FIS) and the PSC Risk Score a marker of liver disease severity constituted the primary outcomes of interest. Co-existent symptoms of insomnia, concentration difficulty, and itching, measured at baseline by the liver symptoms domain of the Quality of Life Survey for Cholestatic Liver Disease (Chol-QOL), were used to determine their relationship with fatigue and disease severity outcomes.

The result of an interim futility analysis conducted on the original clinical trial showed that UDCA was associated with slightly worse clinical outcomes than placebo despite improvement in liver enzymes. These clinical outcomes constituted the main endpoints of the original trial and included development of varices, meeting minimal
listing criteria for liver transplant, liver transplantation, and death. Due to this finding UDCA study treatment was included as a covariate in the analysis of outcomes to determine whether it had any effect on the outcomes.

Linear mixed effects models were used to examine the temporal pattern of fatigue and disease outcomes, to determine the effect of predictors, and to examine the covariation of these outcomes over time.

Four research questions were posed:

1. What is the pattern of change in fatigue and disease severity in chronic liver disease patients over a 5-year period?
2. Do fatigue and disease trajectories differ by gender and by coexistent symptoms at baseline?
3. Do changes in disease severity predict changes in fatigue severity over time?
4. Do trajectories of fatigue and disease severity in chronic liver disease patients covary together over time?

Demographics

This study included a significantly smaller proportion of African Americans compared with the remaining group from the original trial. All African American participants were enrolled at non Mayo-Rochester sites where compliance with fatigue survey administration may have been less.
Patterns of Fatigue and Disease Severity

Fatigue

The first research aim sought to describe patterns of fatigue and disease severity in the study sample. The average fatigue level from the unconditional means model was 29.16, which was comparable to fatigue levels previously reported in PSC (Bjornsson, Simren, Olsson, & Chapman, 2004; Jones, Gray & Newton, 2009) yet notably lower than those reported in PBC patients (Prince, James, Holland, & Jones, 2000; Biagini, et al., 2008). Little change was seen in fatigue scores over the 5-year study period, as the average yearly increase was 1.04 points despite significant variation in individual scores. This is a minimal change in an instrument with a total possible score of 160 points. Stable fatigue patterns in cholestatic liver disease patients have been noted previously by Jones et al. (2006) and more recently by Bjornsson, et al. (2009) with greater levels predictive of liver-related mortality.

No research measuring fatigue as a trajectory could be found in chronic liver disease yet patterns of fatigue have been studied in other chronic conditions. The trajectory of fatigue was studied in rheumatoid arthritis patients and measured on a 0 to 100 scale, with a linear pattern found to be the best fit (Fifield et al., 2001). A longitudinal study examining fatigue in multiple sclerosis as absent, borderline or present at multiple time points found significant variations in these fatigue categories over time (Johnsson, Ytterberg, Hillert, Holmquist, & von Koch, 2007). Fatigue in patients undergoing cancer treatment follows a non-linear trajectory (Miaskowski et al., 2008). Clearly fatigue patterns are subject to the population under study and method of
measurement. Those with chronic liver disease have fatigue that changes minimally over time.

As research shows high fatigue in cholestatic liver disease patients is associated with greater mortality, it is likely that fatigue increases at a point where it distinguishes those at greater risk of mortality. Yet little increase was seen in fatigue levels over the five-year duration of this study. Whether patients in this study with FIS scores greater than 40, a level linked with a mortality risk in PBC, were more likely to have worse disease is not known and was not the purpose of this study. It may be that as PBC and PSC differ in demographic and clinical manifestations, fatigue may not have the same predictive effect in PSC that it does in PBC.

Disease

Risk scores followed a nonlinear trajectory evidenced by the significant positive quadratic effects. The biochemical and clinical components of the risk score worsen over time. Early in the course of the disease aspartate aminotransferase (AST) levels are elevated. With time bilirubin levels rise and albumin levels fall and complications of variceal bleeding may occur (Angulo & Lindor, 1999). PSC is a progressive disease culminating in liver failure or death. Once patients become symptomatic with jaundice from elevated bilirubin levels and variceal bleeding the disease follows a more aggressive course (Talwalkar & Lindor, 2001). Often timing of liver transplantation becomes challenging given the sometimes rapid deterioration of these patients.

No previous research was found on the pattern of change in liver disease severity as measured by risk scores or other disease markers. The risk score is a
surrogate marker of PSC disease severity and survival probability. This research showed disease progresses at an accelerate rate over time which does not match the pattern of the trajectory of fatigue.

**Gender and Symptoms as Predictors of Fatigue and Disease**

The addition of covariates was examined in the linear mixed effects models for fatigue and disease severity with the purpose of identifying inter-individual differences. The fact that no covariates significantly interacted with time indicated that the effect of the covariates only influenced baseline level and not rate of change.

**Gender and fatigue**

Female PSC patients reported significantly greater initial levels of fatigue but their fatigue does not worsen at a greater rate than does that in men. The difference in symptom experience is consistent with other conditions where women have reported greater fatigue and other symptom morbidity than men (Miaskowski, 2004; Baldwin et al., 2009). A review of studies evaluating gender differences in symptoms found that female excess in symptom reporting was found to be independent from the population under study and occurred across the age spectrum (Gijsbers van Wijk & Kolk, 1997). In a study examining gender differences in PSC symptoms, women were shown to suffer more from symptoms of fatigue, itching, abdominal pain and fever than men (Bergquist, Said, & Broome, 2007). In this study 40% of women suffered from fatigue versus 29% of men and 28% of women complained of itching versus 16% of men ($p < .05$). No differences were seen in disease severity. Excess symptom morbidity in women likely is not attributable to more physical morbidity or worse disease.
Mechanisms behind the gender difference in the fatigue experience are not clear. A component of the explanation for higher rates of symptom reporting in women is that there are differences in the way symptoms are perceived, evaluated and acted upon (Macintyre, Ford, & Hunt (1999). Women may have a lower threshold for symptom reporting (Verbrugge, 1985) or a greater readiness to perceive physical sensations as symptoms of illness (Gijsbers van Wijk, van Vliet, Kolk, & Everaerd, 1991). Other theories pertain to the way symptoms are measured. Differences in symptom reporting may be the result of an artifact of measurement. Research by Stommel et al. (1993) found that certain items on the Center for Epidemiologic Studies Depression Scale (CES-D) produced biased responses when comparisons were done of men’s and women’s responses to these items. It is possible that other instruments may have gender bias in items that may artificially raise women’s levels of these symptoms. Research has suggested that women have a more expansive vocabulary for fatigue including such terms as ‘tiredness’, ‘reduced energy’, and ‘lack of vigor’ which may affect the likelihood of fatigue being detected and could argue for use of a sex-specific fatigue taxonomy (Chervin, 2000; Baldwin et al., 2009).

**Gender and disease severity**

Gender had no association with initial risk score indicating that PSC disease severity does not differ in men and women. A handful of studies have been done that support this finding. A comparison of 30 men and 30 women with cholestatic liver disease found little clinical and histological difference between the groups (Rubel,
Rabin, Seeff, Licht, & Cuccherini, 1984). In another study, men with primary biliary cirrhosis had greater elevation in liver biochemistries, more jaundice and more advanced histological stage disease than women but were also significantly older when diagnosed (Muratori et al., 2007). Although women in the current study were more symptomatic than men they did not have worse liver disease.

**Co-existent symptoms and fatigue**

Baseline symptoms of insomnia and concentration difficulty predicted greater levels of fatigue. Poor sleep quality has been linked with daytime fatigue Cauch-Dudek et al. (1998), cognitive dysfunction (Newton, Bhala, Burt, et al. 2006) and excessive daytime somnolence (Newton, Gibson, Tomlinson, et al. 2006) in liver disease patients. There is a shift away from nighttime sleep to daytime sleep, a finding entirely restricted to high fatigued patients, and not related to liver disease severity (Newton, Gibson, Tomlinson, et al.).

These abnormalities in circadian rhythms particularly, daytime somnolence and poor nighttime sleep, have also been found in other fatigue-associated conditions including multiple sclerosis and HIV (Attarian, Brown, Duntley, Carter, & Cross, 2004; Stankoff, et al. 2005; Salahuddin, Barroso, Leserman, Harmon & Pence, 2009). Daytime somnolence wasn’t measured *per se* in the current research but the symptom of concentration difficulty may be the result of this daytime somnolence, which has been identified as a strong predictor of fatigue in previous studies. Sleep disruption with daytime cognitive repercussions and fatigue appears to be independent of liver disease activity and is found in other fatigued conditions. A “cause and effect” scenario may be
possible or as proposed by Swain and Le (1998) a common central pathogenetic process resulting from the inflammation of chronic disease may be to blame.

*Coexistent symptoms and disease*

Predictors of disease severity in the risk score model differed from those significant for fatigue. Of co-existent symptoms only itching was associated with significantly worse initial disease severity. In a natural history study of itching in cholestatic liver disease, alkaline phosphatase, aspartate aminotransferase, bilirubin, albumin, and risk score were found to be significant predictors of itching (Talwalkar, Souto, Jorgensen, & Lindor, 2003). These variables are indicators of disease severity and provide evidence itching is related to disease activity. Itching is associated with indices of disease severity, yet has been shown to spontaneously resolve in some patients as liver failure supervenes (Sherlock, 2000). This may indicate there are inter-individual differences that influence its perception (Jones & Bergasa, 1999) resulting in inconsistent relationships with disease severity. As with fatigue the importance of self-evaluation of symptoms is inherent in their perception and report.

Patients who received the UDCA treatment as compared to those on placebo had a lower overall risk score (-0.284, \( p < .05 \)). The drug is associated with reduction in aspartate aminotransferase (AST) levels one of the factors used to calculate risk score. As UDCA treatment predicted significantly worse clinical outcomes in the original study the effect of this drug on reducing risk score would not be comparable to a reduction in disease severity and is of no real prognostic significance.
**Missing Data Mechanism**

The results of fitting the fatigue model including an indicator variable for those who dropped out of the study showed that the missing data pattern could be missing completely at random (MCAR). The inclusion of the indicator variable as a covariate was not statistically significant nor did it affect the model parameters. As MCAR is an assumption seldom met it may be more realistic to assume that the mechanism for the missing fatigue data is missing at random.

For those missing the disease severity outcome, the indicator variable for the risk score data analysis was statistically significant indicating that patients who dropped out of the study had on average a significantly higher risk score (0.60, \( p < .0001 \)) than those who remained in the study. The significant interaction between the indicator variable and itching showed that patients with itching who dropped out had significantly worse disease severity than those who remained in the study. This increased risk score can be explained by the fact that fourteen of the dropouts were transplanted or died and would have had worse disease severity. The missing data mechanism is clearly not MCAR as the probability that the risk score response is missing is related to the itching covariate and the not yet observed risk score outcomes. The dropout mechanism for risk score is likely not missing at random (NMAR).

**Risk Score as a Time-Varying Predictor of Fatigue**

In order to better clarify the effect of disease on fatigue, risk score was added to the fatigue outcome model to determine its effect as a time varying covariate. The actual varying values of risk score at each time point were included rather than a fixed
baseline value, making it a time varying covariate. This would begin to address the question of whether fatigue and disease co-varied. The addition of risk score as a time varying covariate was not significant implying disease severity likely bears no correlation with fatigue. This finding was not unexpected due to the difference in fatigue and disease patterns of change. It is unlikely that a predictor that increases in a nonlinear pattern would predict an outcome that essentially does not change over time.

**Relationship between Fatigue and Disease Trajectories**

The last aim sought to determine whether there are similarities in fatigue and disease patterns of change. Conventional approaches focusing on analysis of change in one variable at a time do not answer questions of relationships between patterns of change on multiple variables, which can be done with multivariate models.

**Covariates in model for linear fatigue and disease change**

A bivariate model was used to address this research question. The first bivariate model included a linear effect for both outcomes. The effect of the gender, co-existent symptoms, disease duration and UDCA treatment across the two outcomes was determined. Gender, insomnia and concentration difficulty were predictive of fatigue in the bivariate model as in the univariate model for fatigue. In the bivariate model greater disease duration predicted lower fatigue suggesting that patients who have had their liver disease for a longer period of time suffer less fatigue. Although an unexpected finding, the relatively stable pattern of fatigue in these patients and lack of relationship with indicators of disease severity make this finding plausible. Lower perceived fatigue with greater disease duration may be the result of PSC patients adjusting to their fatigue
as a “new normal” level. It is assumed that people have an internal standard for judging their current level of a symptom which remains the same over time. Yet people may adapt to fatigue in chronic illness and come to perceive it as normal. This phenomenon has been defined as a change in the meaning of one’s self-evaluation of the current level of the target construct or subject of investigation (Visser, Smets, Sprangers, & de Haes, 2000).

Itching was found to predict greater fatigue in the bivariate model. Although research has not consistently linked itching with fatigue in liver disease, it could be expected that sleep disruption and fatigue might result from itching. The majority of fatigued patients do not suffer from itching (Cauch-Dudek et al., 1998; Stanca et al., 2005), yet those who do itch may be fatigued. Itching tends to be an episodic symptom with spontaneous resolution in some patients (Olsson et al., 1999). When itching occurs it may certainly exacerbate fatigue or vice versa and disrupt sleep giving rise to increased fatigue.

**Covariation between linear fatigue and disease trajectories**

The first bivariate model used included a linear model for change in both fatigue and risk score outcomes. Relationships between the two outcomes were determined by examining the covariances and correlations between intercepts and slopes of fatigue and disease severity. No significant relationship was found between levels of fatigue and disease or between their rates of linear change. Fatigue in PSC patients does not relate to disease status nor does it increase in relation to disease progression.
The relationship between fatigue and liver disease severity has been studied extensively in the literature yet to date no evidence exists that the two are related. The premise that degree of fatigue would be related to disease severity assumes that symptoms are a direct reflection of pathology. Pennebaker & Epstein (1983) dispute this traditional biomedical model, which assumes a causal or close relationship between physical state and symptoms. They argue that physiological changes from disease are insufficient to explain the symptom experience and an appreciation of the influence of patient beliefs about disease is needed. In this research not only gender but also the existence of other fatigue related symptoms was associated with increased fatigue severity.

Baseline fatigue level and rate of progression were not related. Fatigue levels differ by gender and existence of co-existent symptoms but remain fairly stable over time unlike the disease trajectory. This provided additional evidence that these two outcomes are not strongly related and do not co-vary together.

**Covariates in model for linear fatigue and quadratic disease change**

The addition of a quadratic effect for disease did not alter the significance of the predictor effects in the second bivariate model. Although there was an improved fit in the model, the change in the predictors was subtle. This is likely due to the fact that the covariates were only predictive of baseline levels of fatigue and disease and did not predict degree of change in either outcome.
Covariation between linear fatigue and quadratic disease trajectories

The quadratic effect for risk score improved model fit. Although a significant correlation between the fatigue intercept and disease slope was present, this linear disease effect is not interpretable given there is a significant quadratic effect for disease.

Patients with greater disease severity were more likely to experience rapid increase in progression evidenced by the positive correlation between baseline severity and the quadratic effect for disease. The significant relationship between baseline disease severity and rate of progression indicates that those with more advanced disease may deteriorate more quickly. Most studies of disease progression in PSC have focused on survival analyses; no examination of risk score patterns in these patients over time could be found. It is known that PSC follows a variable and fluctuating course, consistent with the nonlinear nature of decline found in this research, making timing of liver transplant prior to onset of debilitating disease challenging (Wiesner et al., 1992). The close surveillance of PSC patients nearing liver transplant is the result of this potential for rapid deterioration reflecting a disease trajectory that worsens at an accelerated rate.

The lack of a relationship between the intercepts or slopes of the two outcomes indicates level of fatigue and disease are not directly related. Patients with more advanced disease did not have greater fatigue at any one point in time nor did changes in the two outcomes correlate. The risk score includes objective biochemical and clinical measures not subject to patient interpretation and less likely to be affected by measurement error than fatigue. As fatigue is best modeled as linear and disease as
quadratic it is understandable that the two outcomes might not be associated. Yet given the research linking elevated fatigue levels and mortality risk in cholestatic liver disease, it was expected that there might be an association between baseline fatigue and disease severity. This was not the case in this study and is in agreement with previous research reports finding no association between fatigue symptoms and markers of liver disease.

It is clear that despite the prevalence and reported severity of fatigue in cholestatic liver disease and a link with mortality, a direct relationship with specific disease markers is not evident. This could be due to inherent problems with fatigue measurement. Fatigue is highly subjective and difficult to define making its measurement challenging. Although fatigue consists of cognitive and physical sensations, the experience requires self-evaluation, which may differ among individuals (Winningham, 1994). Advances have been made in measuring fatigue with the goal that these self-assessment questionnaires such as the FIS be valid, reproducible and reliable. Yet these fatigue instruments measure subjective fatigue. It may be desirable to supplement self-report questionnaires with objective fatigue assessments, which may correlate better with clinical disease markers such as the Mayo risk score. These objective assessments would provide some validation of self-reported fatigue. More recently an attempt has been made to measure peripheral muscle function manifestations of fatigue in cholestatic liver disease, which would serve as a more objective measure (Hollingsworth et al., 2008). The ability to evaluate fatigue and measure it accurately is clearly the challenge.
Summary

The study examined the relationship between fatigue and disease severity and the role of gender and coexistent symptoms in patients with chronic liver disease over a five-year period. Gender and symptoms of insomnia, concentration difficulty and itching on fatigue and disease severity outcomes were examined in individual models and jointly across both fatigue and disease outcomes.

Fatigue levels in liver disease patients remain stable with little increase over time; however disease progresses at an increasing rate of change. Women and those with insomnia, difficulty with concentration and itching are more likely to suffer from greater levels of fatigue but not worse disease. Evidence of similar relationships has been found in previous research in cholestatic liver disease. The presence of itching and greater disease duration predicted more advanced liver disease. The difference in significant covariates provides evidence that fatigue and disease severity outcomes reflect somewhat different underlying processes. Insomnia and concentration difficulty represent part of a fatigue-related cycle that does not appear to be associated with liver disease severity. Itching and disease duration were associated with disease severity. These results are consistent with results from previous cross-sectional studies.

Examination of the correlation between fatigue and disease over time did not show evidence of an association between levels or related patterns of change in these outcomes.
**Strengths and Limitations**

**Strengths**

Strengths of this research included the longitudinal data spanning more than five years with fairly complete assessments on fatigue and disease. This provided an opportunity to study symptoms and disease markers in patients with a relatively rare type of liver disease. Additional demographic and clinical information allowed analysis of predictors of these fatigue and disease outcomes. As most previous research into predictors of fatigue has been cross-sectional, the longitudinal nature of the study design made it possible to better determine causal relationships.

**Limitations**

As this was a secondary analysis, the study was limited to the data that were previously collected. A prospective study design would have allowed for choice in the selection of variables, specific instruments, and timing of observations. A secondary analysis of data is efficient and economical. This is particularly attractive given the lengthy duration of the study. The data set allowed for an opportunity to evaluate research questions, which would have been impractical if done prospectively.

Another limitation in this study related to the first one is in the instrument used to measure coexistent symptoms. These symptom measurements were taken from the subscale of a disease-specific quality of life measure, the Chol-QOL. The response format for these questions was a four point Likert-type scale. The format was changed to a dichotomous outcome of present or absent for these analyses. Patients completing these symptom questions responded based on the Likert-type format not the...
dichotomous format meaning the validity of the transformed responses is less informative.

Despite a fairly complete set of risk scores, many of the fatigue assessments were missing. Only 116 out of the enrolled 150 patients completed the FIS at the entry visit with 31 out of 61 patients completing the instrument at year 5. The occasional missed assessments were due to non-administration of the instrument, lost questionnaires, or patients failing to complete. Data were also missing on patients who dropped-out of the study for reasons of voluntary withdrawal, non-compliance, liver transplant, and death. Based on statistical analysis, the mechanism for missing fatigue data can be assumed to be MAR which does not pose problems with the validity of model parameters. The missing data mechanism for risk score data is likely NMAR, which threatens the validity of the model parameters, as it is probable that risk scores would be significantly greater in those patients who required liver transplant. Nevertheless, the extent of missing risk score data was small, so confidence in the validity of the model is good.

One of the important results of any study is the ability to generalize the findings to the population of PSC patients. The demographic characteristics of this sample were representative of the known age and gender characteristics of PSC patients reported in the literature. While the sample in this research was from a number of institutions throughout the United States, it represented a convenience sample of patients seen at medical institutions for their liver disease. For this reason they may have differed in unknown ways from PSC patients not seen at these facilities. The study was instituted
as a multicenter study for the specific purpose of increasing the racial and ethnic
diversity of the study sample yet the percent of participants who were not white was
less than 3%.

**Implications for Nursing**

Nurses and others providing care to chronic liver disease patients should be aware that the degree of patient reported fatigue may be out of proportion to liver disease severity. Patients can be reassured that although they have high fatigue, it does not mean their disease is worsening and their prognosis is not worse because of the fatigue. Fatigue has a unique effect on women and appears to impair their quality of life to a greater degree than men. The occurrence of other manifestations of this fatigue such as sleep difficulty and cognitive effects indicate an added symptom burden. Nurses should be cognizant of these fatigue implications in the provision of patient education and counseling.

**Implications for Future Research**

Fatigue is the most common symptom in patients with liver disease and has a more profound impact on women as evidenced in this study. Further research into the mechanisms behind the significant gender differences in fatigue is needed. One area of study could include examination of fatigue instruments for potential gender bias in measurement approaches. Tailored interventions to help women cope with the impact fatigue may have on daily functioning are needed. The relationship between disrupted sleep, cognitive functioning and fatigue should be studied with validated measures to
verify these relationships. Interventions to improve sleep hygiene and help patients adapt to those aspects of cognition impacted by fatigue are needed.

While women suffered greater fatigue there was no evidence that women also had more severe disease however additional follow-up may be needed. Whether greater fatigue in women also results in worse quality of life is another important area of inquiry. Differential symptom and chronic disease manifestations in men and women are poorly understood and should be the subject of continued research.

Multilevel modeling is a useful statistical approach for studying longitudinal symptom data in chronic disease. The analysis in this study provided evidence of significant inter-individual differences in patient reported fatigue and helped to identify characteristics of those most at risk for greater fatigue. Longitudinal studies with this type of statistical analysis can identify patient characteristics important in symptom patterns. These patient characteristics should then be considered as potential covariates or stratification criteria in the design of fatigue intervention studies.
References


*Research in Nursing & Health, 29*, 40-50


Wiesner, R. H., Porayko, M. K., Dickson, E. R., Gores, G. J., LaRusso, N. F., Hay, J.
transplantation in primary biliary cirrhosis and primary sclerosing cholangitis.
Hepatology, 16, 1290-1299.

knowledge. Oncology Nursing Forum, 21, 23-36.

Witt-Sullivan, H., Heathcote, J., Cauch, K., Blendis, L., Ghent, C., Katz, A., Milner,
primary biliary cirrhosis in Ontario, Canada. Hepatology. 12, 98-105.

liver diseases and health-related quality of life. American Journal of
Gastroenterology. 95, 497-502.

Zein, C. O., & Lindor, K. D. (2001). Primary sclerosing cholangitis. Seminars in
Gastrointestinal Disease, 12, 103-112.

decreased survival in primary biliary cirrhosis. GUT, 56, 1165-1166.
Table 1

*Example PSC Patients, Mayo Risk Scores, and Estimated Survival Probability*

<table>
<thead>
<tr>
<th>Age</th>
<th>Albumin* (3.5-5.0)</th>
<th>Bilirubin* (0.6-1.0)</th>
<th>AST* (19-45)</th>
<th>Variceal Bleeding</th>
<th>Risk Score</th>
<th>4-year % survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>4.0</td>
<td>0.9</td>
<td>68</td>
<td>no</td>
<td>0.127</td>
<td>93</td>
</tr>
<tr>
<td>47</td>
<td>3.6</td>
<td>1.4</td>
<td>84</td>
<td>no</td>
<td>0.931</td>
<td>84</td>
</tr>
<tr>
<td>52</td>
<td>3.0</td>
<td>2.6</td>
<td>120</td>
<td>no</td>
<td>2.107</td>
<td>58</td>
</tr>
<tr>
<td>52</td>
<td>3.0</td>
<td>2.6</td>
<td>120</td>
<td>yes</td>
<td>3.494</td>
<td>12</td>
</tr>
</tbody>
</table>

*Albumin is in mg/dl, bilirubin is in g/dl and AST in U/L. Normal ranges are in ( ).
<table>
<thead>
<tr>
<th>Variables</th>
<th>Study patients (n=135)</th>
<th>Original study (n=15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age M (SD)</td>
<td>46.6 (12.8)</td>
<td>44.1 (14.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>77 (57%)</td>
<td>9 (60%)</td>
<td>ns</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>7 (5%)</td>
<td>3 (25%)</td>
<td>.03</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.5 (2%)</td>
<td>0 (0%)</td>
<td>ns</td>
</tr>
<tr>
<td>Risk Score M (SD)</td>
<td>0.32 (0.80)</td>
<td>0.37 (1.05)</td>
<td>ns</td>
</tr>
<tr>
<td>Disease Duration in years</td>
<td>4.9 (6.3)</td>
<td>5.4 (7.0)</td>
<td>ns</td>
</tr>
</tbody>
</table>
### Table 3

*Means (SD), Sample Sizes, and Correlations on Fatigue Assessments over the 5-year period*

<table>
<thead>
<tr>
<th>Visit</th>
<th>Mean (SD)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 0</td>
<td>27.2 (29.1), n=116</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>29.2 (32.9), n=84</td>
<td>0.83*</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td>28.3 (30.7), n=77</td>
<td>0.85*</td>
<td>0.88*</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 3</td>
<td>26.4 (29.7), n=67</td>
<td>0.71*</td>
<td>0.81*</td>
<td>0.79*</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 4</td>
<td>28.3 (34.8), n=43</td>
<td>0.80*</td>
<td>0.85*</td>
<td>0.74*</td>
<td>0.77*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Year 5</td>
<td>25.2 (35.0), n=31</td>
<td>0.73*</td>
<td>0.89*</td>
<td>0.88*</td>
<td>0.82*</td>
<td>0.93*</td>
<td>-</td>
</tr>
</tbody>
</table>

*p < .001
Table 4

Means (SD), Sample Sizes and Correlations on the PSC Risk Scores over the 5 year period

<table>
<thead>
<tr>
<th>Visit</th>
<th>Mean (SD)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 0</td>
<td>0.32 (0.80), n=135</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>0.14 (0.87), n=122</td>
<td>0.80*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td>0.28 (0.86), n=117</td>
<td>0.74*</td>
<td>0.85*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 3</td>
<td>0.33 (0.97), n=108</td>
<td>0.65*</td>
<td>0.74*</td>
<td>0.79*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 4</td>
<td>0.44 (1.09), n=99</td>
<td>0.67*</td>
<td>0.73*</td>
<td>0.84*</td>
<td>0.84*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 5</td>
<td>0.55 (1.11), n=61</td>
<td>0.58*</td>
<td>0.55*</td>
<td>0.71*</td>
<td>0.76*</td>
<td>0.84*</td>
<td></td>
</tr>
</tbody>
</table>

*p < .001
Table 5

Unconditional Means and Growth Models for the Fatigue Data (n=135)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No change model</th>
<th>Linear Model</th>
<th>Quadratic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed Effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>$\gamma_0$</td>
<td>29.16 (2.53)**</td>
<td>27.78 (2.52)**</td>
</tr>
<tr>
<td>Time (linear term)</td>
<td>$\gamma_1$</td>
<td>1.05~</td>
<td>1.46(1.31)</td>
</tr>
<tr>
<td>Time$^2$ (quadratic term)</td>
<td>$\gamma_2$</td>
<td>-0.09(0.28)</td>
<td></td>
</tr>
<tr>
<td><strong>Variance Components</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level-1 Within-person</td>
<td>$\sigma_\epsilon^2$</td>
<td>197.06(16.43)**</td>
<td>174.16(16.72)**</td>
</tr>
<tr>
<td>Initial status</td>
<td>$\sigma_0^2$</td>
<td>777.02(105.54)**</td>
<td>712.63(104.83)**</td>
</tr>
<tr>
<td>Linear term</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>variance</td>
<td>$\sigma_1^2$</td>
<td>6.38(3.74)*</td>
<td>7.48e-16</td>
</tr>
<tr>
<td>covariance with initial status</td>
<td>$\sigma_{01}$</td>
<td>23.71(17.41)</td>
<td>38.22(50.58)</td>
</tr>
<tr>
<td>Quadratic term</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>variance</td>
<td>$\sigma_2^2$</td>
<td>0</td>
<td>-2.67(10.84)</td>
</tr>
<tr>
<td>covariance with initial status</td>
<td>$\sigma_{02}$</td>
<td></td>
<td>0.68(0.410~)</td>
</tr>
<tr>
<td>covariance with linear term</td>
<td>$\sigma_{12}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fit criteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2LogLikelihood</td>
<td>3766.8</td>
<td>3754.1</td>
<td>3753.3</td>
</tr>
<tr>
<td>AIC</td>
<td>3772.8</td>
<td>3766.1</td>
<td>3769.3</td>
</tr>
<tr>
<td>BIC</td>
<td>3781.5</td>
<td>3783.5</td>
<td>3792.5</td>
</tr>
</tbody>
</table>

Note ~p<.10; * p<.05; **p<.01; ***p<.001
Table 6

Unconditional Means and Growth Models for the PSC Risk Score Data (n=135)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No change</th>
<th>Linear change model</th>
<th>Quadratic model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed Effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>$\gamma_{00}$</td>
<td>0.383 (0.074)***</td>
<td>0.212 (0.068)**</td>
</tr>
<tr>
<td>Time (linear term)</td>
<td>$\gamma_{10}$</td>
<td>0.096 (0.018)***</td>
<td>-0.028 (0.034)</td>
</tr>
<tr>
<td>Time$^2$ (quadratic term)</td>
<td>$\gamma_{20}$</td>
<td>0.029 (0.008)***</td>
<td></td>
</tr>
<tr>
<td>Variance Components</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level-1 Within-person</td>
<td>$\sigma_{e}^2$</td>
<td>0.260 (0.016)***</td>
<td>0.161 (0.012)***</td>
</tr>
<tr>
<td>Level-2 Initial status</td>
<td>$\sigma_{0}^2$</td>
<td>0.665 (0.090)**</td>
<td>0.517 (0.076)***</td>
</tr>
<tr>
<td>Linear term</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>variance</td>
<td>$\sigma_{1}^2$</td>
<td>0.026 (0.006)***</td>
<td>0.052 (0.024)*</td>
</tr>
<tr>
<td>covariance with initial status</td>
<td>$\sigma_{01}$</td>
<td>0.034 (0.016)*</td>
<td>0.011(0.035)</td>
</tr>
<tr>
<td>Quadratic term</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>variance</td>
<td>$\sigma_{2}^2$</td>
<td>0.002 (0.001)*</td>
<td></td>
</tr>
<tr>
<td>covariance with initial status</td>
<td>$\sigma_{02}$</td>
<td>0.007(0.008)</td>
<td></td>
</tr>
<tr>
<td>covariance with linear term</td>
<td>$\sigma_{12}$</td>
<td>-0.007(0.005)</td>
<td></td>
</tr>
<tr>
<td>Fit criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2LogLikelihood</td>
<td>1304.2</td>
<td>1166.2</td>
<td>1143.7</td>
</tr>
<tr>
<td>AIC</td>
<td>1310.2</td>
<td>1178.2</td>
<td>1163.7</td>
</tr>
<tr>
<td>BIC</td>
<td>1318.9</td>
<td>1195.6</td>
<td>1192.7</td>
</tr>
</tbody>
</table>

Note ~p<.10; * p<.05; **p<.01; ***p<.001
Table 7

Comparison of (REML) log-likelihoods and AIC for the Covariance Pattern Models for Fatigue

<table>
<thead>
<tr>
<th>Covariance Pattern Model</th>
<th>-2 (REML) Log Likelihood</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstructured</td>
<td>3472.9</td>
<td>3480.9</td>
</tr>
<tr>
<td>Compound symmetry</td>
<td>3590.8</td>
<td>3594.8</td>
</tr>
<tr>
<td>Autoregressive</td>
<td>3590.8</td>
<td>3594.8</td>
</tr>
</tbody>
</table>
Table 8

*Comparison of the (REML) log-likelihoods and AIC for the Covariance Pattern Models for PSC Risk Score Data*

<table>
<thead>
<tr>
<th>Covariance Pattern Model</th>
<th>-2 (REML) Log Likelihood</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstructured</td>
<td>1108.1</td>
<td>1116.1</td>
</tr>
<tr>
<td>Compound symmetry</td>
<td>1215.6</td>
<td>1221.6</td>
</tr>
<tr>
<td>Autoregressive</td>
<td>1215.6</td>
<td>1221.6</td>
</tr>
</tbody>
</table>
Table 9
Linear Mixed Effect Model for Fatigue ($n=135$)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Final Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed Effects</strong></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>$\gamma_{00}$</td>
</tr>
<tr>
<td></td>
<td>13.08 (3.02)***</td>
</tr>
<tr>
<td>Time (linear term)</td>
<td>$\gamma_{10}$</td>
</tr>
<tr>
<td></td>
<td>1.04 (0.54)~</td>
</tr>
<tr>
<td>Gender</td>
<td>$\gamma_{01}$</td>
</tr>
<tr>
<td></td>
<td>10.83 (4.10)**</td>
</tr>
<tr>
<td>Insomnia</td>
<td>$\gamma_{02}$</td>
</tr>
<tr>
<td></td>
<td>9.10 (4.41)*</td>
</tr>
<tr>
<td>Concentration</td>
<td>$\gamma_{03}$</td>
</tr>
<tr>
<td></td>
<td>25.60 (5.54)**</td>
</tr>
<tr>
<td><strong>Variance Components</strong></td>
<td></td>
</tr>
<tr>
<td>Level-1</td>
<td>$\sigma^2_e$</td>
</tr>
<tr>
<td>Within-person</td>
<td>165.26 (16.29)**</td>
</tr>
<tr>
<td>Level-2</td>
<td>$\sigma^2_0$</td>
</tr>
<tr>
<td>Initial status</td>
<td>485.88 (79.43)***</td>
</tr>
<tr>
<td><strong>Linear term</strong></td>
<td></td>
</tr>
<tr>
<td>variance</td>
<td>$\sigma^2_1$</td>
</tr>
<tr>
<td></td>
<td>6.18 (3.68) *</td>
</tr>
<tr>
<td>covariance with initial status</td>
<td>$\sigma_{01}$</td>
</tr>
<tr>
<td></td>
<td>21.08 (15.21)</td>
</tr>
<tr>
<td><strong>Fit criteria</strong></td>
<td></td>
</tr>
<tr>
<td>-2LogLikelihood</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3491.6</td>
</tr>
<tr>
<td>AIC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3509.6</td>
</tr>
<tr>
<td>BIC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3535.1</td>
</tr>
</tbody>
</table>

Note ~p<.10; * p<.05; **p<.01; ***p<
Table 10

*Linear Mixed-Effect Model for PSC Risk Scores (n=135)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Final Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed Effects</td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>$\gamma_{00}$</td>
</tr>
<tr>
<td>Time (linear term)</td>
<td>$\gamma_{10}$</td>
</tr>
<tr>
<td>Time$^2$ (quadratic term)</td>
<td>$\gamma_{20}$</td>
</tr>
<tr>
<td>Insomnia</td>
<td>$\gamma_{01}$</td>
</tr>
<tr>
<td>Itching</td>
<td>$\gamma_{02}$</td>
</tr>
<tr>
<td>Disease duration</td>
<td>$\gamma_{03}$</td>
</tr>
<tr>
<td>UDCA treatment</td>
<td>$\gamma_{04}$</td>
</tr>
<tr>
<td>Variance Components</td>
<td></td>
</tr>
<tr>
<td>Level-1 Within-person</td>
<td>$\sigma_e^2$</td>
</tr>
<tr>
<td>Level-2 Initial status</td>
<td>$\sigma_0^2$</td>
</tr>
<tr>
<td>Linear term variance</td>
<td>$\sigma_1^2$</td>
</tr>
<tr>
<td>covariance with initial status</td>
<td>$\sigma_{01}$</td>
</tr>
<tr>
<td>Quadratic term variance</td>
<td>$\sigma_2^2$</td>
</tr>
<tr>
<td>covariance with initial status</td>
<td>$\sigma_{02}$</td>
</tr>
<tr>
<td>covariance with linear term</td>
<td>$\sigma_{12}$</td>
</tr>
<tr>
<td>Fit criteria</td>
<td></td>
</tr>
<tr>
<td>-2LogLikelihood</td>
<td></td>
</tr>
<tr>
<td>AIC</td>
<td></td>
</tr>
<tr>
<td>BIC</td>
<td></td>
</tr>
</tbody>
</table>

*Note ~p<.10; * p<.05; **p<.01; ***p<.001*
Table 11

Model for Fatigue with PSC Risk Score as a Time-Varying Covariate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Final Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed Effects</strong></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>$\gamma_{00}$</td>
</tr>
<tr>
<td>Time (linear term)</td>
<td>$\gamma_{10}$</td>
</tr>
<tr>
<td>Gender</td>
<td>$\gamma_{01}$</td>
</tr>
<tr>
<td>Insomnia</td>
<td>$\gamma_{02}$</td>
</tr>
<tr>
<td>Concentration</td>
<td>$\gamma_{03}$</td>
</tr>
<tr>
<td>Risk Score</td>
<td>$\gamma_{04}$</td>
</tr>
<tr>
<td><strong>Variance Components</strong></td>
<td></td>
</tr>
<tr>
<td>Level-1</td>
<td>$\sigma_e^2$</td>
</tr>
<tr>
<td>Level-1-2</td>
<td>$\sigma_0^2$</td>
</tr>
<tr>
<td>Linear term</td>
<td></td>
</tr>
<tr>
<td>variance</td>
<td>$\sigma_1^2$</td>
</tr>
<tr>
<td>covariance with initial status</td>
<td>$\sigma_{01}$</td>
</tr>
<tr>
<td><strong>Fit criteria</strong></td>
<td></td>
</tr>
<tr>
<td>-2LogLikelihood</td>
<td>3493.5</td>
</tr>
<tr>
<td>AIC</td>
<td>3513.5</td>
</tr>
<tr>
<td>BIC</td>
<td>3541.8</td>
</tr>
</tbody>
</table>

Note: ~p<.10; * p<.05; **p<.01; ***p<.001
Table 12

*Estimates of Fixed Effects for Multilevel Model of Linear Change in Fatigue and Disease*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fatigue Severity</th>
<th>Disease Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameter</td>
<td>SE</td>
</tr>
<tr>
<td>Fixed Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.429**</td>
<td>0.128</td>
</tr>
<tr>
<td>Linear term</td>
<td>0.033~</td>
<td>0.018</td>
</tr>
<tr>
<td>Gender</td>
<td>0.214~</td>
<td>0.128</td>
</tr>
<tr>
<td>Concentration</td>
<td>0.928***</td>
<td>0.167</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.170</td>
<td>0.150</td>
</tr>
<tr>
<td>Itching</td>
<td>0.293*</td>
<td>0.146</td>
</tr>
<tr>
<td>Disease duration</td>
<td>-0.037**</td>
<td>0.014</td>
</tr>
<tr>
<td>UDCA treatment</td>
<td>0.156</td>
<td>0.137</td>
</tr>
</tbody>
</table>

**Fit Criteria**

- **-2 Log Likelihood**: 1884.1
- **AIC**: 1938.4
- **BIC**: 2015.0

~ p < .10, * p < .05, ** p < .01, *** p < .001
Table 13.

*Estimates of Random Effects for Multilevel Model of Linear Change in Fatigue and Disease*

Variance, Covariances, and Intercorrelations of Random Intercepts and Slopes

<table>
<thead>
<tr>
<th></th>
<th>Fatigue Intercept</th>
<th>Disease Intercept</th>
<th>Fatigue Slope</th>
<th>Disease Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatigue Intercept</strong></td>
<td>0.452*** (0.076)</td>
<td>0.023 (0.054)</td>
<td>0.022 (0.015)</td>
<td>0.021 (0.017)</td>
</tr>
<tr>
<td><strong>Disease Intercept</strong></td>
<td>0.050 (0.073)</td>
<td>0.452*** (0.016)</td>
<td>0.014 (0.017)</td>
<td>0.038* (0.017)</td>
</tr>
<tr>
<td><strong>Fatigue Slope</strong></td>
<td>0.416 (0.004)</td>
<td>0.261 (0.004)</td>
<td>0.006~ (0.004)</td>
<td>-0.003 (0.004)</td>
</tr>
<tr>
<td><strong>Disease Slope</strong></td>
<td>0.175 (0.007)</td>
<td>0.328* (0.007)</td>
<td>-0.205 (0.007)</td>
<td>0.030*** (0.007)</td>
</tr>
</tbody>
</table>

Numbers in the upper right triangle and diagonal are covariances and standard errors, and the lower triangle contains the correlations.
Table 14

*Estimates of Fixed Effects for Multilevel Model of Linear Change in Fatigue and Quadratic Change in Disease*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fatigue Severity</th>
<th>Disease Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameter</td>
<td>SE</td>
</tr>
<tr>
<td>Fixed Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.470***</td>
<td>0.126</td>
</tr>
<tr>
<td>Linear term</td>
<td>0.035*</td>
<td>0.017</td>
</tr>
<tr>
<td>Quadratic term</td>
<td>0.031***</td>
<td>0.009</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>0.244*</td>
<td>0.124</td>
</tr>
<tr>
<td>Concentration difficulty</td>
<td>0.965***</td>
<td>0.164</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.132</td>
<td>0.147</td>
</tr>
<tr>
<td>Itching</td>
<td>0.303*</td>
<td>0.143</td>
</tr>
<tr>
<td>Disease duration</td>
<td>-0.039**</td>
<td>0.013</td>
</tr>
<tr>
<td>UDCA treatment</td>
<td>0.229</td>
<td>0.134</td>
</tr>
<tr>
<td>Fit Criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2 Log Likelihood</td>
<td>1855.1</td>
<td></td>
</tr>
<tr>
<td>AIC</td>
<td>1921.1</td>
<td></td>
</tr>
<tr>
<td>BIC</td>
<td>2014.7</td>
<td></td>
</tr>
</tbody>
</table>

~ p < .10, * p < .05, ** p < .01, *** p < .001
### Table 15

*Estimates of Random Effects for Multilevel Model of Linear Change in Fatigue and Quadratic Change in Disease*

<table>
<thead>
<tr>
<th></th>
<th>Fatigue Intercept</th>
<th>Disease Intercept</th>
<th>Fatigue Slope</th>
<th>Disease Slope</th>
<th>Disease Quadratic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatigue Intercept</strong></td>
<td>0.473***</td>
<td>-0.019</td>
<td>0.019</td>
<td>0.091*</td>
<td>-0.015~</td>
</tr>
<tr>
<td>$u_{0ik}$</td>
<td>(0.078)</td>
<td>(0.058)</td>
<td>(0.015)</td>
<td>(0.036)</td>
<td>(0.008)</td>
</tr>
<tr>
<td><strong>Disease Intercept</strong></td>
<td>-0.038</td>
<td>0.503***</td>
<td>0.017</td>
<td>-0.029</td>
<td>0.019*</td>
</tr>
<tr>
<td>$u_{0ij}$</td>
<td>(0.085)</td>
<td>(0.017)</td>
<td>(0.041)</td>
<td>(0.009)</td>
<td></td>
</tr>
<tr>
<td><strong>Fatigue Slope</strong></td>
<td>0.338</td>
<td>0.300</td>
<td>0.007*</td>
<td>-0.009</td>
<td>0.001</td>
</tr>
<tr>
<td>$u_{1ik}$</td>
<td>(0.004)</td>
<td>(0.008)</td>
<td>(0.002)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease Slope</strong></td>
<td>0.558*</td>
<td>-0.172</td>
<td>-0.474</td>
<td>0.056*</td>
<td>-0.008</td>
</tr>
<tr>
<td>$u_{1ij}$</td>
<td>(0.027)</td>
<td>(0.005)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease Quadratic</strong></td>
<td>-0.429~</td>
<td>0.512*</td>
<td>0.320</td>
<td>-0.688</td>
<td>0.003*</td>
</tr>
<tr>
<td>$u_{2ij}$</td>
<td></td>
<td>(0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Numbers in the upper right triangle and diagonal are covariances and standard errors, and the lower triangle contains the correlations.
Figure 1
Fatigue Severity (Fatigue Impact Scores) over the 5-year period
Figure 2
Disease Severity (Mayo Risk Score) over the 5-year period
Figure 3
Trellis Graphs of Fatigue Trajectories in a Subset of Patients
Figure 4
Trellis Graphs of Disease Trajectories in a Subset of Patients
Figure 5

Mean Standardized Scores for Fatigue and Disease Severity Outcomes

![Graph showing mean standardized scores for fatigue and disease severity outcomes across visits.](image-url)
APPENDIX A

FISK FATIGUE IMPACT SCALE

Because of my fatigue:

1. I feel less alert

   0               1               2               3               4
   No             Small           Moderate         Big            Extreme
   Problem       Problem       Problem        Problem        Problem

2. I feel that I am more isolated from social contact

   0               1               2               3               4
   No             Small           Moderate         Big            Extreme
   Problem       Problem       Problem        Problem        Problem

3. I have to reduce my workload and responsibilities

   0               1               2               3               4
   No             Small           Moderate         Big            Extreme
   Problem       Problem       Problem        Problem        Problem

4. I am more moody

   0               1               2               3               4
   No             Small           Moderate         Big            Extreme
   Problem       Problem       Problem        Problem        Problem

5. I have difficulty paying attention for a long period of time

   0               1               2               3               4
   No             Small           Moderate         Big            Extreme
   Problem       Problem       Problem        Problem        Problem
6. I feel like I cannot think clearly

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem</td>
<td>No</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
</tr>
</tbody>
</table>

7. I work less effectively (work inside or outside the home)

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem</td>
<td>No</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
</tr>
</tbody>
</table>

8. I have to rely more on others to help me or do things for me

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem</td>
<td>No</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
</tr>
</tbody>
</table>

9. I have difficulty planning activities ahead of time

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem</td>
<td>No</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
</tr>
</tbody>
</table>

10. I am more clumsy and uncoordinated

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem</td>
<td>No</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
</tr>
</tbody>
</table>

11. I find that I am more forgetful

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem</td>
<td>No</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
</tr>
</tbody>
</table>

12. I am more irritable and more easily angered

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem</td>
<td>No</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
</tr>
</tbody>
</table>
13. I have to be careful about pacing my physical activities

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
<td></td>
</tr>
<tr>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td></td>
</tr>
</tbody>
</table>

14. I am less motivated to do anything that requires physical effort

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
<td></td>
</tr>
<tr>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td></td>
</tr>
</tbody>
</table>

15. I am less motivated to engage in social activities

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
<td></td>
</tr>
<tr>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td></td>
</tr>
</tbody>
</table>

16. My ability to travel outside my home is limited

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
<td></td>
</tr>
<tr>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td></td>
</tr>
</tbody>
</table>

17. I have trouble maintaining physical effort for long periods

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
<td></td>
</tr>
<tr>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td></td>
</tr>
</tbody>
</table>

18. I find it difficult to make decisions

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
<td></td>
</tr>
<tr>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td></td>
</tr>
</tbody>
</table>
19. I have few social contacts outside of my own home

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Problem</td>
<td>No Problem</td>
<td>Moderate Problem</td>
<td>Big Problem</td>
<td>Extreme Problem</td>
<td></td>
</tr>
</tbody>
</table>

20. Normal day-today events are stressful for me

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Problem</td>
<td>No Problem</td>
<td>Moderate Problem</td>
<td>Big Problem</td>
<td>Extreme Problem</td>
<td></td>
</tr>
</tbody>
</table>

21. I am less motivated to do anything that requires thinking

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Problem</td>
<td>No Problem</td>
<td>Moderate Problem</td>
<td>Big Problem</td>
<td>Extreme Problem</td>
<td></td>
</tr>
</tbody>
</table>

22. I avoid situations that are stressful for me

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Problem</td>
<td>No Problem</td>
<td>Moderate Problem</td>
<td>Big Problem</td>
<td>Extreme Problem</td>
<td></td>
</tr>
</tbody>
</table>

23. My muscles feel much weaker than they should

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Problem</td>
<td>No Problem</td>
<td>Moderate Problem</td>
<td>Big Problem</td>
<td>Extreme Problem</td>
<td></td>
</tr>
</tbody>
</table>

24. My physical discomfort is increased

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Problem</td>
<td>No Problem</td>
<td>Moderate Problem</td>
<td>Big Problem</td>
<td>Extreme Problem</td>
<td></td>
</tr>
</tbody>
</table>
25. I have difficulty dealing with anything new

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Small</th>
<th>Moderate</th>
<th>Big</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
</tr>
</tbody>
</table>

26. I am less able to finish tasks that require thinking

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Small</th>
<th>Moderate</th>
<th>Big</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
</tr>
</tbody>
</table>

27. I feel unable to meet the demands that people place on me

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Small</th>
<th>Moderate</th>
<th>Big</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
</tr>
</tbody>
</table>

28. I less able to provide financial support for myself and my family

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Small</th>
<th>Moderate</th>
<th>Big</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
</tr>
</tbody>
</table>

29. I engage in less sexual activity

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Small</th>
<th>Moderate</th>
<th>Big</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
</tr>
</tbody>
</table>

30. I find it difficult to organize my thoughts when I am doing things at home or work

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Small</th>
<th>Moderate</th>
<th>Big</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
</tr>
</tbody>
</table>
31. I am less able to complete tasks that require physical effort

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Problem</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
</tr>
<tr>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td></td>
</tr>
</tbody>
</table>

32. I worry about how I look to other people

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Problem</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
</tr>
<tr>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td></td>
</tr>
</tbody>
</table>

33. I am less able to deal with emotional issues

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Problem</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
</tr>
<tr>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td></td>
</tr>
</tbody>
</table>

34. I feel slowed down in my thinking

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Problem</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
</tr>
<tr>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td></td>
</tr>
</tbody>
</table>

35. I find it hard to concentrate

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Problem</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
</tr>
<tr>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td></td>
</tr>
</tbody>
</table>

36. I have difficulty participating fully in family activities

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Problem</td>
<td>Small</td>
<td>Moderate</td>
<td>Big</td>
<td>Extreme</td>
</tr>
<tr>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td></td>
</tr>
</tbody>
</table>
37. I have to limit physical activities

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Problem</td>
<td>Small</td>
<td>Problem</td>
<td>Moderate</td>
<td>Problem</td>
</tr>
<tr>
<td>Problem</td>
<td></td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
</tr>
</tbody>
</table>

38. I require more frequent and longer periods of rest

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Problem</td>
<td>Small</td>
<td>Problem</td>
<td>Moderate</td>
<td>Problem</td>
</tr>
<tr>
<td>Problem</td>
<td></td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
</tr>
</tbody>
</table>

39. I am not able to provide as much emotional support to my family as I should

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Problem</td>
<td>Small</td>
<td>Problem</td>
<td>Moderate</td>
<td>Problem</td>
</tr>
<tr>
<td>Problem</td>
<td></td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
</tr>
</tbody>
</table>

40. Minor difficulties seem like major difficulties

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Problem</td>
<td>Small</td>
<td>Problem</td>
<td>Moderate</td>
<td>Problem</td>
</tr>
<tr>
<td>Problem</td>
<td></td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
<td>Problem</td>
</tr>
</tbody>
</table>
APPENDIX B

Quality of Life Survey for Cholestatic Liver Disease Patients
Dear Patient:

To better understand how you feel about your general health, we would like to ask you to fill out the questionnaire. Please fill out the form as honestly as you can, describing how you have felt and how well you have been able to function.

This is a research study. Filling out this form is voluntary. If you decide how to participate in this study, your care will not be compromised in any way. If you do not want to answer certain questions, you may cross them out. Obviously, the more complete answers we get, the more information we may have to study. Please let us know if you have any questions while filling out the questions.

Thank you for your participation.

Quality of life survey in cholestatic liver disease.

[ ] I do not wish to participate further in this survey
Instructions: Please check the appropriate box or fill in the blank as indicated.

Study ID_____________________________________

Name_______________________________________

What is today’s date _____/_____/___________

1. How would you rate your overall health at the present time? (Check one)
   ___ Excellent     ___ Good     ___ Fair     ___ Poor

2. During the past month, how much body pain have you had (Check one).
   ___ None     ___ Mild     ___ Moderate     ___ Severe

3. During the past month, how many days have you been sick in bed for at least part of the day?
   ____________ days

4. Does your health keep you from working for pay or from being a homemaker or from going to school? (Check one)
   ___ Yes     ___ No

5. Are you limited in the kind or amount of work for pay, housework or school work you can do because of your health? (Check one)
   ___ Yes     ___ No

6. Does your health currently limit the kind of vigorous activities that you can do, such as running, heavy lifting, sports? (Check one)
   ___ Yes     ___ No

7. Do you now have any trouble walking several blocks or climbing a few flights of stairs because of your health? (Check one)
   ___ Yes     ___ No
8. Do you now have any trouble walking a single block or climbing one flight of stairs because of your health? (Check one)
   ___Yes   ___No

9. Do you currently have trouble bending, lifting or stooping because of your health?
   ___Yes   ___No

10. Here are some words and phrases which we would like you to use to best describe how you feel about your present life. For example, if you think your present life is very “boring”, put an X on the line right next to the word “boring”. If you think it is very “interesting”, put an X on the line right next to the word “interesting”. If you think it is somewhere in between put an X on the line where you think it belongs. Put an X in one line for every set of responses.

   Boring      ___    ___    ___    ___    ___    ___    ___    Interesting

   Enjoyable   ___    ___    ___    ___    ___    ___    ___    Miserable

   Useless     ___    ___    ___    ___    ___    ___    ___    Worthwhile

   Friendly    ___    ___    ___    ___    ___    ___    ___    Lonely

   Full        ___    ___    ___    ___    ___    ___    ___    Empty

   Discouraging ___    ___    ___    ___    ___    ___    ___    Hopeful

   Disappointing ___    ___    ___    ___    ___    ___    ___    Rewarding

   Brings out the best in me ___    ___    ___    ___    ___    ___    Doesn’t give me much of a chance
11. Is your present state of health causing problems with your:
   (Check one for each question.)

   Job or work (that is: paid employment)  ____ Yes  ____ No

   Looking after the home
   (ex: cleaning, cooking, doing odd jobs)  ____ Yes  ____ No

   Social like (ex: going out, seeing friends,
   going to a show)  ____ Yes  ____ No

   Home life (that is: relationships with
   Other people in your home)  ____ Yes  ____ No

   Sex life  ____ Yes  ____ No

   Interests and hobbies (ex: sports, arts and
   crafts, do-it-yourself)  ____ Yes  ____ No

   Vacations (ex: summer or winter vacations,
   weekends away)  ____ Yes  ____ No

12. Which of the eight following statements best describes your state of health,
   How you feel and your level of activity? (Check one).

   ____ Normal; no complaints, no evidence of disease
   ____ Able to carry out normal activity; minor symptoms
   ____ Able to carry out normal activity with effort, some symptoms
   ____ Able to care for myself but unable to carry on normal activity or active work
   ____ Requiring occasional assistance but able to care for most of my needs
   ____ Requiring considerable assistance and frequent medical care
   ____ Disabled; requiring special care and assistance
   ____ Worse off than any of these statements suggest
13. Below is a list of problems and complaints that people sometimes have. Please read each item carefully and check the box on the right hand side that best indicates how much you were distressed by each symptom during the past month. Check only one box for each item.

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue or lack of energy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excess appetite or overeating</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint aches or pains</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pains</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeplessness/Insomnia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood swings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling depressed or sad</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trembling or shakiness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased interest in sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impotence (men only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor or blurred vision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in facial appearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruising or fragile skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching of skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
14. Taking all things together, how would you say things are these days? Would you say you’re: (Check one)

____ Very happy        ____ Pretty happy        ____ Not too happy

15. Overall, how satisfied are you with your health at the present time? (Check one)

____ Completely satisfied
____ Very satisfied
____ Satisfied
____ Neutral
____ Dissatisfied
____ Very dissatisfied
____ Completely dissatisfied

16. All things considered, how satisfied are you with your life as a whole these days?

____ Completely satisfied
____ Very satisfied
____ Satisfied
____ Neutral
____ Dissatisfied
____ Very dissatisfied
____ Completely dissatisfied

Any further comments you might have would be most welcome.

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________