ELSEVIER

Women's Health Issues 18 (2008) 336–342

WOMEN'S HEALTH ISSUES

FATIGUE AS A MAJOR PREDICTOR OF QUALITY OF LIFE IN WOMEN WITH AUTOIMMUNE LIVER DISEASE

The Case of Primary Biliary Cirrhosis

Ellen D. Sogolow, PhD[a], Judith N. Lasker, PhD[a]*, and Lynn M. Short, PhD, MPH[b,c]

[a]*Department of Sociology and Anthropology, Lehigh University, Bethlehem, Pennsylvania*
[b]*Analytic Systems Associates, Snellville, Georgia*
[c]*School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina*

Received 8 June 2007; accepted 17 December 2007

Objectives. **Fatigue is a nearly universal symptom of many chronic diseases, yet it is often poorly understood and underappreciated as a factor in quality of life (QOL). Generally, clinicians have relied on subjective measures of fatigue, if they consider it at all. This study uses well-validated instruments to examine fatigue as a predictor of QOL in women with primary biliary cirrhosis (PBC), an autoimmune, chronic liver disease.**

Methods. **Eighty-one women with PBC completed a survey that included measures of fatigue (Fatigue Impact Scale) and QOL (SF-36) as well as demographic variables (age, education) and medical information (symptoms, stage of illness, time since diagnosis). QOL results for the sample were compared with those of a nationally normed U.S. population. Bivariate and multivariate analyses were conducted to identify contributors to variation in QOL.**

Results. **Compared with national norms, QOL for this PBC population was significantly impaired. When all variables with bivariate significance in relation to QOL were included in multivariate analyses, results showed fatigue to be the primary predictor of QOL, including all 8 QOL scales and the 2 summary scales. Regression results, dominated by fatigue, explain 25–59% of the variance in QOL.**

Conclusions. **Fatigue has profound effects on every aspect of life for women with PBC—physical, social, emotional, and psychological. The results lead to recommendations for health care providers to assess fatigue in their patients with PBC and to take steps, where warranted, to mitigate its effects.**

Liver disease is the 7th leading cause of death among Americans 25–64 years of age (Minino, 2004). One chronic liver condition, called primary biliary cirrhosis (PBC), is found predominantly in people aged 40–65; 90% are women. PBC is a rare autoimmune disease in which the body attacks the cells lining the liver's bile ducts, causing inflammation and destruction. The cause of PBC is thought to be related to viral, environmental, and/or genetic causes (National Institutes of Health [NIH], 2005; Selmi et al., 2004). Liver transplantation is the only current solution for treating end-stage PBC, although women with PBC may live for years with the disease before requiring transplantation.

Autoimmune disorders, including PBC, rank among the top 10 causes of death of U.S. women in every age group under 65. The NIH report asserts that "autoimmune diseases . . . represent a significant physical, emotional, social, and fiscal burden to the country's health care system" (NIH, 2005). These diseases are generally poorly recognized and not well researched. As a result, women who experience the symptoms of autoimmune disease are often misdiag-

Supported by internal research funding through Lehigh University.

* Correspondence to: Dr. Judith Lasker, Lehigh University, Department of Sociology and Anthropology, 681 Taylor Street, Bethlehem, PA 18015. Phone: 610-758-3811; fax: 610-758-6552.

E-mail: Judith.Lasker@lehigh.edu

1049-3867/08 $-See front matter.
doi:10.1016/j.whi.2007.12.005

nosed and must fight for recognition that they have a "real" disease (Dumit, 2006; Richman, Jason, Taylor, & Jahn, 2000).

Contributing to the misdiagnosis of PBC and other autoimmune diseases is that a major symptom—fatigue—is operating in a disease that targets women predominantly. Women who report fatigue are too often not taken seriously (Dumit, 2006).

As demonstrated by studies in Canada, The Netherlands, and the United Kingdom (Goldblatt et al., 2002; Huet, Deslauriers, Tran, Faucher, & Charbonneau, 2000; Newton, Bhala, Burt, & Jones, 2006; Prince, James, Holland, & Jones, 2000; Witt-Sullivan et al., 1990), among others, fatigue is a highly prevalent symptom among people with PBC. One study, for example, showed that fatigue is greater in persons who have PBC than in matched community controls or in persons with autoimmune hepatitis (Goldblatt et al., 2002).

Fatigue in general, and specifically in relationship to chronic liver disease, remains poorly understood. Until recently, fatigue has not been measured with psychometric precision, perhaps recognized as a subjective report but lacking clinical validation (Jones, 2004). In addition, there is little evidence for an association between fatigue and histologic markers of liver disease (Huet et al., 2000; Miller, Hiller, & Shaw, 2001; Jones, 1995). As 1 study argues, fatigue in people with PBC is not well studied because it is difficult to get society to appreciate that fatigue is a "real" symptom, and because it is difficult to quantify (Goldblatt et al., 2002). Yet fatigue may be the most disabling symptom experienced by persons with chronic liver disease.

Although some studies have addressed quality of life (QOL) in chronic liver disease, there has been a paucity of such research for people with PBC (Martin, Sheridan, & Younossi, 2002; Rannard, Buck, Jones, James, & Jacoby, 2004). Yet, QOL has been shown to be significantly compromised in people with cholestatic liver disease (Younossi, Kiwi, Boparai, Price, & Guyatt, 2000), and in people with liver disease who are awaiting transplant (Gross et al., 1999).

We know that fatigue is common in many chronic illnesses, yet we have little information about the relationship of fatigue to overall QOL or to the various dimensions of QOL among people with PBC, other autoimmune diseases, or other chronic liver diseases. A few recent studies suggest there is a relationship; however, the researchers did not use validated measures of fatigue (Newton et al., 2006; Poupon, Chretien, Chazouilleres, Poupon, & Chwalow, 2004). Stanca et al. (2005) used the Fatigue Impact Scale (FIS) and found correlations between fatigue and dimensions of QOL as measured by the Mayo version of the NIDDK-QA, but they also found fatigue to be less prevalent than seen in other PBC studies. A recent effort to develop a PBC-specific QOL measure incorporated fatigue as 1 of 6 domains (Jacoby et al., 2005). Yet, arguably, locating fatigue as an outcome may confound understanding its role as a predictor (Newton et al., 2006).

The aims of this paper are to examine QOL in women with PBC, comparing their results with national norms; to assess the relationship of fatigue to QOL, using widely accepted and well-validated measures; and to consider the relative impact of fatigue on QOL when other important factors—symptoms and stage of disease—are taken into account. Our key hypothesis is that fatigue is a significant predictor of QOL, and when considered in multivariate analyses, fatigue will remain a strong explanatory factor.

Methods

In the current study, participants are women with PBC who attended the biannual conference of the PBCers Organization, held in Biloxi, Mississippi, in May, 2003. Permission for the study was obtained from the Institutional Review Board of Lehigh University, with protocol number 03-118, and the Board of Directors of the PBCers Organization, an Internet-based organization with >2,400 members worldwide (www.pbcers.org/).

We distributed the survey at the time that attendees picked up their registration materials when they arrived at the conference. They were given a consent form and a questionnaire (in a separate packet from registration) and were asked to complete them if they were willing, and to return them to a box in the registration area before the end of the conference. The authors were available to answer questions if needed.

The survey included demographic items (age, education), self-reports of stage of illness (histologic stage ranging from 1 to 4 as determined by liver biopsy, with stage 4 indicating the presence of cirrhosis), and years since diagnosis, as well as the FIS (Fisk et al., 1994), and the SF-36 QOL instrument (Ware & Dewey, 2000). We also listed possible symptoms of PBC and asked if the participant had experienced any of them in the past 60 days. This time frame was used to optimize inclusion of information on infrequent events such as bleeding. The symptoms listed were ascites (fluid in abdomen, which can become infected), bleeding problems, encephalopathy (confusion and cognitive dysfunction caused by toxic substances entering the brain), fatigue, itching, liver cancer, osteoporosis, varices (swollen vessels in the esophagus), and leg swelling. We used total symptoms to characterize, in an approximate way, the severity of living with PBC.

The FIS has 40 items distributed across 3 scales: 10 cognitive items, 10 physical items, and 20 social items. Subjects were asked to indicate on a 5-point Likert

scale (from 0 for "no problem" to 4 for "extreme problem") the extent to which fatigue had caused problems for them in the past 30 days. This instrument is designed such that total FIS is the sum of the 3 scales. It has been validated with diseases associated with fatigue (chronic fatigue syndrome and multiple sclerosis) and not associated with fatigue (hypertension; Fisk et al., 1994); it has also been validated specifically with people who have PBC (Prince et al., 2000). When analysis called for a comparison of FIS with total symptoms, we omitted the self-report of fatigue from the list of symptoms.

The SF-36 is a measure that has been widely used with studies of illness, including liver disease (Rannard et al., 2004; Unal et al., 2001; Bravata, Olkin, Barnato, Keeffe, & Owens, 1999). It has 8 scales (Physical Functioning, Role—Physical, Body Pain, General Health, Vitality, Social Functioning, Role—Emotional, and Mental Health) as well as 2 summary measures (Physical Component Summary and Mental Component Summary). Results, with higher scores indicating better QOL, can be compared to U.S. national norms established separately by gender and age.

We scored SF-36 QOL data using the standard protocol (Ware et al., 2000). We then compared results against national normed data for women in the 55–64 age group, the closest to the mean for this sample of women with PBC, using a Pascal program developed by one of the authors (L.M.S.) to examine the comparisons statistically. All other analyses—frequencies, Pearson correlations, *t*-tests, and stepwise linear regression—were carried out in SPSS.

Results

Description of the Sample

Of the approximately 100 people with PBC who attended the conference in Biloxi, 81 women completed the survey. Table 1 describes this group. On average, the group members knew of their diagnosis for 6.24 years, with a range of <1 to 27 years. Most participants (61.3%) were in their 40s or 50s, and 41.8% had graduated college or gone on to postgraduate education. They were approximately evenly divided between the early stages (1–2) and later stages (3–4) of PBC.

Symptoms

Participants reported a range of 0–8 major symptoms, with a mean of 3.01. Most frequent were fatigue (84.0%) and pruritus (itching; 56.8%), followed by osteoporosis (33.3%), leg swelling (28.4%), bleeding problems (27.2%), encephalopathy (18.5%), ascites (13.6%), varices (9.1%), and liver cancer (2.5%).

Table 1. Description of Sample

Characteristic	Number	Percent of Sample
Age (n = 80), yrs		
<40	6	6.3
41–50	15	18.8
51–60	34	42.5
≥61	25	31.3
Education (n = 79)		
High school education or less	14	17.7
Some college	32	40.5
College graduate	14	17.7
Post-college	19	24.1
Stage of illness (n = 64)		
1	17	26.6
2	18	28.2
3	11	17.2
4	18	28.1
Years since diagnosis (n = 79),* yrs		
≤3	31	39.2
3.5–10	33	40.6
≥11	15	19.0

*Average number of years since diagnosis is 6.24.

Fatigue

FIS-Total averaged 67.44 (of a potential maximum score of 160; standard deviation [SD], 39.36), composed of means of 18.17 (SD, 10.72) for the cognitive scale and 19.58 (SD, 10.27) for the physical scale (each of which has a maximum possible score of 40), and 29.69 (SD, 20.44) for the social scale (which has a maximum possible score of 80). FIS-Total scores are significantly higher for those who reported fatigue as a symptom (mean, 74.14, compared with 32.38 for those who did not report fatigue as a symptom: $t = -4.97$; $p < .001$).

Quality of Life

Table 2 provides the SF-36 results for the PBC sample and for normed data from the most comparable U.S. population group (women 55–64; Ware et al., 2000). Scale scores for the PBC sample ranged from 37.15 for General Health to 45.40 for Mental Health. The summary scores showed poorer QOL for the Physical Component Summary (38.61) than for the Mental Component Summary (44.38). When compared with national norms, the women in the PBC sample are significantly lower in QOL across all scales and summary scores.

Bivariate Analyses

We examined relationships between the 8 SF-36 scales and 2 summary measures on the one hand and the variables we expected to influence variations in QOL on the other: fatigue (as measured by the FIS scales and FIS-Total), stage of illness (1–4), years since diagnosis, age, education, and Total Symptoms (Table 3). Years since diagnosis and educational level were not associated with SF-36 scales or summary components

Table 2. Quality of Life (SF-36) Scales, Means, Standard Deviations, and Ranges, Comparing People With PBC With U.S. Norms

	PBC Sample (n = 81)			National Norms, Females 55–64 (n = 647)			Significance	
S-F 36 Scale	Mean	SD	Range	Mean	SD	Range	*t*-value	*p*
Physical functioning	40.22	10.19	14.94–57.03	46.26	11.07	14–58	4.67	<.0001
Role—physical	39.34	11.23	17.67–56.85	47.78	10.98	17–57	6.51	<.0001
Body pain	42.23	9.45	28.31–45.21	47.73	11.09	19–63	4.27	<.0001
General health	37.15	10.15	18.61–62.47	48.98	10.93	18–64	9.25	<.0001
Vitality	41.36	10.31	20.87–61.46	50.16	10.90	20–71	6.89	<.0001
Social functioning	41.63	12.09	13.22–56.85	49.31	11.07	13–57	5.82	<.0001
Role—emotional	42.01	13.04	9.23–55.88	49.16	11.06	9–56	5.37	<.0001
Mental health	45.40	10.65	16.22–64.09	50.19	10.75	10–65	3.78	.0002
Physical component summary	38.61	9.61	18.97–55.59	46.79	11.18	4–66	6.30	<.0001
Mental component summary	44.38	11.29	16.47–62.19	50.95	10.70	9–70	5.18	<.0001

(data not in Table 3). Age was weakly but significantly associated with the General Health and Social Functioning scales, as well as with the Mental Component Summary; older people in the sample had higher scores than younger people. All FIS subscales, the FIS-Total score, and Total Symptoms were inversely and significantly correlated with all SF-36 scales and the 2 summary measures ($p < .001$). Correlations ranged from −.401 (FIS-Cognitive with Physical Functioning) to −.735 (FIS-Total with Social Functioning). Stage of illness was significantly and negatively related to Role—Physical, Body Pain, General Health, Vitality, and Social Functioning and to both summary measures. Total Symptoms was highly related to all scales and the 2 summary measures, with more symptoms being associated with significantly reduced QOL.

To understand the relative contributions of the significant variables—FIS scales, stage of illness, age, and Total Symptoms—to QOL, multiple regressions were carried out with the 8 SF-36 scales and 2 summary scales as the dependent variables. Results from the multiple regressions (Table 4) show that fatigue is a significant predictor of all SF-36 scales and both summary measures. The percentage of the variance in QOL explained in these equations ranges from 25–59%. In most cases, the FIS-P, representing limitations in physical activity owing specifically to fatigue, is the best predictor. In the case of the Mental Component Summary, Role—Emotional, and Mental Health, FIS-S is the relevant predictor. Thus the inability to participate in social activities as a result of fatigue is the most important contributor to poor QOL in the arena of mental health. FIS-C only appears in the equation with Physical Functioning as the dependent variable, and surprisingly in a positive direction (more cognitive impairment owing to fatigue is associated with better physical functioning after controls for the other variables). Stage of illness was a significant predictor only for the Vitality scale. Age contributed positively to General Health and Social Functioning, and total number of symptoms did not predict any SF-36 scales.

Discussion and Conclusions

With population changes showing an increase in older adults as well as an increase in prevalence of autoimmune disorders (NIH, 2005), both phenomena disproportionately affecting women, the issue of chronic illness and its impact on QOL is vital to an understanding of women's well-being. Chronic

Table 3. Correlations of Fatigue Impact Score (FIS), Stage, Total Symptoms, and Age With Quality of Life (SF-36) and Scales

Quality of Life	FIS—Cognitive	FIS—Physical	FIS—Social	FIS—Total	Stage	Total Symptoms	Age
Physical functioning	−.401***	−.664***	−.503***	−.544***	−.146	−.437***	−.095
Role—physical	−.602***	−.679***	−.664***	−.686***	−.334**	−.362**	.103
Body pain	−.477***	−.663***	−.580***	−.604***	−.223	−.310**	.104
General health	−.489***	−.635***	−.576***	−.598***	−.319*	−.374**	.273*
Vitality	−.565***	−.717***	−.676***	−.693***	−.396**	−.318**	.183
Social functioning	−.613***	−.726***	−.728***	−.735***	−.270*	−.395***	.245*
Role—emotional	−.473***	−.498***	−.524***	−.531***	−.197	−.369**	.125
Mental health	−.501***	−.520***	−.626***	−.598***	−.165	−.259*	.087
Physical component summary	−.461***	−.707***	−.548***	−.594***	−.268*	−.372**	.046
Mental component summary	−.559***	−.563***	−.661***	−.644***	−.257*	−.309**	.238*

*$p < .05$; **$p < .01$; ***$p < .001$.

Table 4. Multiple Regression: Quality of Life (SF-36) Summary Scores and Scales, With Fatigue Impact Scale (FIS) Subscales (Physical, Social, Cognitive), Stage of Illness, Total Symptoms,* and Age as Independent Variables

			Significant Predictors	
Quality of Life: Dependent Variable	ANOVA	Adjusted R^2	Beta	*p*
Physical functioning	$F = 35.42$; $p = .000$	.466	FIS-P: −.887	.000
			FIS-C: .278	.037
Role—physical	$F = 67.54$; $p = .000$	.457	FIS-P: −.681	.000
Body pain	$F = 62.63$; $p = .000$	.438	FIS-P: −.667	.000
General health	$F = 30.83$; $p = .000$	.433	FIS-P: −.615	.000
			age: .204	.020
Vitality	$F = 49.89$; $p = .000$	.556	FIS-P: −.674	.000
			stage: −.208	.009
Social functioning	$F = 56.63$; $p = .000$	.585	FIS-P −.733	.000
			age: .198	.008
Role—emotional	$F = 27.43$; $p = .002$	.251	FIS-S: −.510	.000
Mental health	$F = 47.27$; $p = .000$	.372	FIS-S: −.617	.000
Physical component summary	$F = 5.96$; $p = .000$	.493	FIS-P: −.707	.000
Mental component summary	$F = 56.04$; $p = .000$	.417	FIS-S: −.651	.000

*Total symptoms did not predict any aspect of QOL.

illness affects both physical and emotional well-being (Morewitz, 2007). PBC, a relatively rare autoimmune disorder affecting primarily women in their middle years, is emblematic of challenges facing many women.

QOL, as measured by the SF-36, is compromised in all 8 domains for women with PBC compared with national norms for a comparable age group. Fatigue explains a large portion of this deficit in QOL; Total Symptoms is not a factor nor is stage of illness, except in predicting the Vitality scale of the SF-36.

Because fatigue frequently has been dismissed—considered too subjective, not associated with clinical markers of disease, and perhaps discounted as a woman's "complaint"—this symptom has been too often neither understood nor appreciated. Indeed, it has often been ignored, with notable exceptions in the case of PBC (Bergasa, 2004; Newton et al., 2006). Medical professionals have been found to downplay conditions such as chronic fatigue syndrome and fibromyalgia, which are predominantly found in women (Asbring & Narvanen 2003). Richman et al. (2000) and Jones (2004) add that physicians may be reluctant to pay attention to fatigue because of the lack of treatments to ameliorate it. The current study demonstrates that fatigue has profound effects on every aspect of life—social, psychological, emotional, and physical—even more than the specific physical markers represented by stage of illness and symptoms. Thus, it is crucial that fatigue in people with PBC, as well as in other chronic diseases that are typified by fatigue, be acknowledged and assessed, and efforts made to alleviate it.

Although there is broad consensus that fatigue is a common symptom of PBC, researchers continue to examine fatigue only as an outcome, even including a domain for fatigue in a recent PBC-specific instrument (Jacoby et al., 2005). This view may lead to or reinforce the expectation that treatment of fatigue requires focus on something else, such as changes in laboratory results. Because such clinical markers appear to be unrelated, the frustration with treatment of fatigue may be reinforced.

A recent study raised a question about whether U.S. persons with PBC might have less fatigue than previously observed in non-U.S. PBC populations (Stanca et al., 2005). In this Biloxi study, however, levels of fatigue are comparable with the non-U.S. results for people with PBC. Also, because this study used the SF-36, QOL in women with PBC relative to national norms can be demonstrated. Given the correlation between fatigue and QOL, the diminished QOL compared with a nationally normed population provides concurrent validity for the diminished fatigue findings.

This study is subject to 3 limitations. First, because these findings are based on a convenience sample of those who attended a conference for persons with PBC, they may be biased in certain ways. For instance, arguably, people with PBC who attend a conference may be less fatigued than their counterparts who are not well enough to travel. On the other hand, persons who are more ill may be more motivated to attend a conference that features expert speakers. To clarify how typical this sample is (or is not), we compared descriptive data on fatigue and FIS scores in this population with that available from other studies.

The proportion of people in this study reporting fatigue as a symptom (80%) is comparable with the average (78%) from 4 major studies that recruited participants with PBC (Cauch-Dudek, Abbey, Stewart, & Heathcote, 1998; Huet et al., 2000; Wanless, Heathcote, & Cauch, 1993; Witt-Sullivan et al., 1990). These

studies found frequencies of fatigue at 68%, 76%, 81%, and 85%, respectively.

The mean score for the total FIS in the current study was 67.44, similar to the 59.6 found in a clinic sample of 116 people with PBC (based on 1.49 average scale score, which we converted into 59.6 when computed for all 40 items; Huet et al., 2000). Another comparison of the FIS is based on the median, which was 66.5 for this study, midway between the FIS reports of 2 other studies, one that used the FIS with a community-based sample of 136 people with PBC in northern England and reported a median score of 40 (Goldblatt et al., 2002) and another with a sample of 58 people with PBC recruited through a hospital clinic and a PBC organization, reporting a median of 78.0 (Prince et al., 2000). Thus, the current sample has similar proportion of participants with the fatigue symptom as other studies that reported on this condition, and mean and median FIS scores similar to or within the range reported by other studies.

A second limitation is the small size of the current sample. It is possible that a larger population is needed to ascertain additional relationships that were not apparent here. For research involving a rare disease such as PBC, however, this sample of 81 is larger than that used in many other studies and has been adequate to support these analyses in all instances.

Third, this study did not consider other factors that also may be relevant to QOL. For instance, medication side effects, depression, and other comorbidities may confound both fatigue and QOL, but were not examined in this study. Also, socioeconomic status and health insurance may be important factors to examine, especially if they impact eligibility for transplant.

Three implications follow from findings of fatigue as a strong predictor of QOL in women with PBC. First, physicians may consider adding a precise and valid measure of fatigue as part of their pretransplant evaluations. This would support long-term evaluation and management. The FIS has several advantages compared with usual evaluation methods: 1) Fatigue is a nearly universal symptom of PBC, so that the FIS instrument would be a specific test for many patients; 2) The FIS score is independent of what can be determined by liver function tests and, thus, provides a multiple measure for evaluation; 3) Use of the FIS does not require acute life-threatening symptoms such as ascites or encephalopathy before instruments are sufficiently sensitive to observe the event; and 4) the FIS is a self-administered, brief paper-and-pencil instrument that can be readily completed during the office visit. As such, the FIS is low cost and potentially high benefit.

Second, the health care team can intervene to treat the ongoing fatigue. The team may refer persons with PBC to occupational and physical therapists who can teach them healthier ways to adapt to fatigue-induced limitations. Rather than withdrawal from events involving physical efforts, occupational therapists may assist persons with PBC to find alternative ways to carry out at least some activities of daily living. Similarly, referrals to physical therapists may provide training to remediate the loss of muscle strength that often accompanies PBC and the adaptations to living with PBC.

Longitudinal studies with regular assessments of fatigue and QOL in people with PBC are needed to identify better the course of this disease and its disabling effects. For instance, a recent follow-up study by Jones et al. (2006) of 136 people with PBC who were assessed in 2000 identified 28 who had subsequently died, and revealed that those with higher levels of fatigue in 2000 were more likely to die in the subsequent years.

Until recent years, fatigue was an acceptable criterion for transplantation for PBC in the United States, and it remains so in some other countries. Longitudinal study with well-validated instruments would allow evidence-based decision making when allocation committees review policies and procedures. The role of fatigue in other autoimmune disorders and chronic ailments, particularly those targeting women, also should receive much greater attention.

Acknowledgments

The authors thank Brendan McGuire, MD, for his review and helpful comments on an earlier draft of the manuscript; Lehigh University for financial support; the PBCers Organization and members for participation in the research; Sarah Kaye and Misty Curreli for assistance with data analysis; Carlos Tavares, Jacqueline Seltzer, and Erica Nastasi for help with manuscript preparation; and the anonymous reviewers for their thoughtful critiques.

References

Asbring, P., & Närvänen, A. L. (2003). Ideal versus reality: Physicians' perspectives on patients with chronic fatigue syndrome (CFS) and fibromyalgia. *Social Science and Medicine*, 57, 711–720.

Bergasa, N. V. (2003). Pruritis and fatigue in primary biliary sclerosis. *Clinical Gastroenterology and Hepatology*, 1, 249–251.

Bergasa, N. V. (2004). Pruritus in chronic liver disease: Mechanisms and treatment. *Current Gastroenterology Reports*, 6, 10–16.

Bravata, D. M., Olkin, I., Barnato, A. E., Keeffe, E. B., & Owens, D. K. (1999). Health-related quality of life after liver transplantation: A meta-analysis. *Liver Transplantation and Surgery*, 5, 318–331.

Cauch-Dudek, K., Abbey, S., Stewart, D. E., & Heathcote, E. J. (1998). Fatigue in primary biliary cirrhosis. *Gut*, 43, 705–710.

Dumit, J. (2006). Illnesses you have to fight to get: Facts as forces in uncertain, emergent illnesses. *Social Science and Medicine*, 62, 577.

Fisk, J. D., Ritvo, P. G., Ross, L., Haase, D. A., Marrie, T. J., & Schlech, W. F. (1994). Measuring the functional impact of fatigue: Initial validation of the fatigue impact scale. *Clinical Infectious Diseases*, 18(Suppl. 1), s79–s83.

Goldblatt, J., Taylor, P. J., Lipman, T., Prince, M. I., Baragiotta, A., Bassendine, M. F., et al. (2002). The true impact of fatigue in

primary biliary cirrhosis: A population study. *Gastroenterology*, 122, 1235–1241.

Gross, C. R., Malinchoc, M., Kim, W. R., Evans, R. W., Wiesner, R. H., Petz, J. L., et al. (1999). Quality of life before and after liver transplantation for cholestatic liver disease. *Hepatology*, 29, 356–364.

Huet, P. M., Deslauriers, J., Tran, A., Faucher, C., & Charbonneau, J. (2000). Impact of fatigue on the quality of life of patients with primary biliary cirrhosis. *American Journal of Gastroenterology*, 95, 760–767.

Jacoby, A., Rannard, A., Buck, D., Bhala, N., Newton, J. L., James, O. F., et al. (2005). Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. *Gut*, 54, 1622–1629.

Jones, D. E., Bhala, N., Burt, J., Goldblatt, J., Prince, M., & Newton, J. L. (2006). Four year follow up of fatigue in a geographically defined primary biliary cirrhosis patient cohort. *Gut*, 55, 536–541.

Jones, E. A. (1995). Fatigue associated with chronic liver disease: A riddle wrapped in a mystery inside an enigma. *Hepatology*, 22, 1606–1608.

Jones, E. A. (2004). Fatigue complicating chronic liver disease. *Metabolic Brain Disease*, 19, 421–429.

Martin, L. M., Sheridan, M. J., & Younossi, Z. M. (2002). The impact of liver disease on health-related quality of life: A review of the literature. *Current Gastroenterology Reports*, 4, 79–83.

Miller, E. R., Hiller, J. E., & Shaw, D. R. (2001). Quality of life in HCV-infection: Lack of association with ALT levels. *Australian New Zealand Journal of Public Health*, 25, 355–361.

Minino, A. M. (2004). Deaths: Preliminary data for 2004. *Center for Disease Control*, 54.

Morewitz, S. J. (2007). *Aging and chronic disorders*. Berlin: Springer-Verlag.

National Institutes of Health, Autoimmune Diseases Coordinating Committee. (2005). Progress in autoimmune diseases research. Available: www3.niaid.nih.gov/. Accessed December 3, 2007.

Newton, J. L., Bhala, N., Burt, J., & Jones, D. E. (2006). Characterisation of the associations and impact of symptoms in primary biliary cirrhosis using a disease specific quality of life measure. *Journal of Hepatology*, 44, 776–783.

Poupon, R. E., Chretien, Y., Chazouilleres, O., Poupon, R., & Chwalow, J. (2004). Quality of life in patients with primary biliary cirrhosis. *Hepatology*, 40, 489–494.

Prince, M. I., James, O. F., Holland, N. P., & Jones, D. E. (2000). Validation of a fatigue impact score in primary biliary cirrhosis: Towards a standard for clinical and trial use. *Journal of Hepatology*, 32, 368–373.

Rannard, A., Buck, D., Jones, D. E., James, O. F., & Jacoby, A. (2004). Assessing quality of life in primary biliary cirrhosis. *Clinical Gastroenterology and Hepatology*, 2, 164–174.

Richman, J. A., Jason, L. A., Taylor, R. R., & Jahn, S. C. (2000). Feminist perspectives on the social construction of chronic fatigue syndrome. *Health Care for Women International*, 21, 173–185.

Selmi, C., Mayo, M. J., Bach, N., Ishibashi, H., Invernizzi, P., Gish, R. G., et al. (2004). Primary biliary cirrhosis in monozygotic and dizygotic twins: Genetics, epigenetics, and environment. *Gastroenterology*, 127, 485–492.

Stanca, C. M., Bach, N., Krause, C., Tandon, N., Freni, M. A., Gutierrez, J. A., et al. (2005). Evaluation of fatigue in US patients with primary biliary cirrhosis. *American Journal of Gastroenterology*, 100, 1104–1109.

Unal, G., de Boer, J., Borsboom, G., Brouwer, J., Essink-Bot, M., & de Man RA. (2001). A psychometric comparison of health-related quality of life measures in chronic liver disease. *Journal of Clinical Epidemiology*, 54, 587–596.

Wanless, I. R., Heathcote, E. J., & Cauch, K. (1993). Detailed histologic grading as a predictor of morbidity and mortality in primary biliary cirrhosis. *Hepatology*, 18, A174.

Ware, J. E., K, & Dewey. (2000). *How to score version 2 of SF-36 health survey*. Lincoln, RI: QualityMetric Inc.

Witt-Sullivan, H., Heathcote, J., Cauch, K., Blendis, L., Ghent, C., Katz, A., et al. (1990). The demography of primary biliary cirrhosis in Ontario, Canada. *Hepatology*, 12, 98–105.

Younossi, Z. M., Kiwi, M. L., Boparai, N., Price, L. L., & Guyatt, G. (2000). Cholestatic liver diseases and health-related quality of life. *American Journal of Gastroenterology*, 95, 497–502.

Author Descriptions

Dr. Ellen Sogolow is a social psychologist and served as adjunct research faculty at Lehigh University during the time of this study.

Dr. Judith Lasker, a sociologist, is professor and chair, Department of Sociology and Anthropology, Lehigh University.

Dr. Lynn Short is the executive director and senior scientist of Analytic Systems Associates, Inc., providing research methods and evaluation and statistical consulting to universities, government agencies, and others.