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Nonalcoholic fatty liver disease: quality of life, exercise intensity and histological severity

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SAN DIEGO STATE UNIVERSITY

Nonalcoholic Fatty Liver Disease:
Quality of Life, Exercise Intensity and Histological Severity

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Public Health (Epidemiology)

by

Kristin David Kistler

Committee in charge:

University of California, San Diego

Professor Theodore Ganiats, Chair
Professor Jeffrey Schwimmer, Co-chair
Professor Kevin Patrick

San Diego State University

Professor Ming Ji
Professor Caroline Macera
Professor James Sallis

2009
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The Dissertation of Kristin David Kistler is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Co-Chair

Chair

University of California, San Diego
San Diego State University

2009
DEDICATION

This dissertation is dedicated to my husband Erik.
Mon amour, ma vie,
Thank you.
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LIST OF ABBREVIATIONS

Introduction:

NAFLD: Nonalcoholic fatty liver disease

NASH: Nonalcoholic steatohepatitis

FFAs: Free fatty acids

QOL: Quality of life

DHHS: Department of Health and Human Services (DHHS)

USDA: U.S. Department of Agriculture

Chapter 1:

NAFLD: Nonalcoholic fatty liver disease

NASH: Nonalcoholic steatohepatitis

QOL: Quality of life

HCV: Hepatitis C virus

HBV: Hepatitis B virus

NASH CRN: Nonalcoholic Steatohepatitis Clinical Research Network

NIDDK: National Institute of Diabetes & Digestive & Kidney Diseases
BMI: Body mass index

SF-36: Short form 36

PCS: Physical component score

MCS: Mental component score

ANOVA: Analysis of variance

Chapter 2:

NAFLD: Nonalcoholic fatty liver disease

NASH: Nonalcoholic steatohepatitis

QOL: Quality of life

NASH CRN: Nonalcoholic Steatohepatitis Clinical Research Network

BMI: Body mass index

ANOVA: Analysis of variance

Chapter 3:

NAFLD: Nonalcoholic fatty liver disease

NASH: Nonalcoholic steatohepatitis

NASH CRN: Nonalcoholic Steatohepatitis Clinical Research Network
BMI: Body mass index

ANOVA: Analysis of variance

DHHS: Department of Health and Human Services (DHHS)

USDA: U.S. Department of Agriculture

MET: Metabolic equivalent

AST: Aspartate aminotransferase

ALT: Alanine aminotransferase

HDL: High density lipoprotein

LDL: Low density lipoprotein
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Finally, I’d like to thank Erik Kistler for the unwavering support he provided throughout this project, and for his patience in repeatedly explaining biochemistry to me. Thank you also to my family for their support and belief that I would some day finish.

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Lake JR, David KM, Steffen BJ, Chu AH, Gordon RD, Wiesner RH: Addition of MMF to dual immunosuppression does not increase the risk of malignant short-term


ABSTRACT OF THE DISSERTATION

Nonalcoholic Fatty Liver Disease:
Quality of Life, Exercise Intensity and Histological Severity

by

Kristin David Kistler

Doctor of Philosophy in Public Health (Epidemiology)

University of California, San Diego 2009
San Diego State University, 2009

Professor Theodore Ganiats, Chair
Professor Jeffrey Schwimmer, Co-Chair

Nonalcoholic fatty liver disease (NAFLD) is a significant public health problem. An estimated 30% of adults and 10% of children are affected, making NAFLD the most common chronic liver disease in the United States. However, there is an incomplete understanding of this disease. The association between NAFLD and quality of life (QOL) remains unclear. These data are important to estimate the burden of illness in NAFLD. Also unclear is the association between exercise and NAFLD severity. These data are important given that exercise is recommended as primary treatment for NAFLD.
Individuals with biopsy-proven NAFLD, enrolled in the NASH CRN, were included in these analyses. Chapter 1 reports QOL in adults with NAFLD. Chapter 2 reports QOL in children with NAFLD. Chapter 3 reports the association between exercise intensity and NAFLD histological severity.

Both adults (n=713) and children (n=240) with NAFLD had a significant decrement in QOL, especially physical health, compared to reference populations without NAFLD. Increased NAFLD severity was associated with poorer physical health in adults while QOL did not significantly differ based on severity in children. In children, symptoms accounted for almost half of the variance in QOL scores, especially fatigue, trouble sleeping, and sadness.

A total of 609 individuals with NAFLD were included in the study of exercise intensity and histological severity. Participants who met the U.S. DHHS/USDA physical activity recommendation for vigorous physical activity (≥75 min/week) had a decreased odds of steatohepatitis, and individuals who met the ‘additional health benefits’ recommendation for vigorous physical activity (≥150 min/week) had a decreased odds of advanced fibrosis. No significant associations were found between moderate-intensity physical activity and histological severity.

Adults and children with NAFLD have a significant decrement in QOL. In children, symptoms are a major determinant of impaired QOL. Strategies to improve QOL, especially physical health, should be a focus for clinicians treating patients with NAFLD. These results also suggest that current exercise treatment recommendations for NAFLD may be insufficient. Collectively these studies expand the understanding
of NAFLD and highlight avenues for further research. Implications of the results are discussed in greater detail within each of the respective chapters.
Introduction: Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) was first described in 1980 (1), since that time there has been increasing recognition that NAFLD is a significant public health problem. Owing largely to the obesity epidemic, NAFLD is now the most common chronic liver condition in the United States (U.S.). Estimates based on U.S. data suggest a prevalence rate of as high as 34% (2). Determining the true prevalence of NAFLD is complicated; liver biopsy provides the only definitive diagnosis of NAFLD, and the invasiveness and cost of a liver biopsy complicate its being used as a diagnostic tool in the general population. Data on the incidence of NAFLD in the U.S. are lacking.

By definition, NAFLD refers to the accumulation of fat, primarily triglycerides, in ≥ 5% of hepatocytes (3). Liver biopsy is the gold standard for diagnosis and is the only diagnostic method that can definitively identify NAFLD. However, ultrasound, computed tomography, and elevated liver enzymes are often used as surrogate markers of NAFLD. The histological features of NAFLD are similar to those seen with liver disease due to excessive alcohol intake. As a result, diagnosis of NAFLD is clinicopathological and excessive alcohol intake (~ >20 g/day) precludes a NAFLD diagnosis. NAFLD comprises a spectrum of liver pathology including simple steatosis, nonalcoholic steatohepatitis (NASH) (inflammation), and cirrhosis (scarring) (Figure I.1). As the severity of NAFLD increases, so does morbidity, and advanced fibrosis is a risk factor for progression to liver failure.
In adults, women are most frequently diagnosed with NAFLD (4). However, this likely represents a bias that women are more likely to go to the doctor than men (and hence get diagnosed with NAFLD), and that men traditionally drink more alcohol than women and therefore get excluded from a diagnosis based on alcohol intake. Increasing age is associated with an increased prevalence of NAFLD as well. For race-ethnicity, the lowest rates of NAFLD are seen in African Americans (5) and the highest in Asians and Hispanics, with Caucasians in between (5,6). In children NAFLD is more common in boys than girls (7), and appears to be most common in Hispanics (8,9). The greatest recognized risk factors for NAFLD are insulin resistance (10) and obesity, particularly central adiposity (11).

The pathogenesis of NAFLD is incompletely understood. Steatosis results from dysregulation of hepatic lipid metabolism. Over abundance of free fatty acids
(FFAs) in the liver (potentially resulting from over-nutrition and/or insulin resistance) results in a disruption of normal lipid metabolism whereby the rate of uptake and/or synthesis of FFAs is less than the rate at which they are stored in hepatocytes (12). Increased production of pro-inflammatory cytokines and decreased anti-inflammatory and insulin-sensitizing cytokines are hypothesized to play an important role in the progression from simple steatosis to steatohepatitis (13).

Current treatment guidelines endorse diet modification for weight loss and physical activity. However, little data are available on the effectiveness of diet and physical activity in reducing NAFLD severity. Drug therapies (most aimed at increasing insulin sensitivity) are currently being tested as well.
Introduction

References


Chapter 1: Quality of Life in Adults with Nonalcoholic Fatty Liver Disease:
Baseline Data from the NASH CRN

1.1 Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the United States. The association between NAFLD and quality of life (QOL) remains unclear. These data are important to estimate the burden of illness in NAFLD. The aim was to report QOL scores of adults with NAFLD, and examine the association between NAFLD severity and QOL.

QOL data were collected from adults with NAFLD enrolled in the NASH Clinical Research Network using the SF-36 survey and scores were compared to normative U.S. population scores. Liver biopsy histology was reviewed by a central pathology committee.

A total of 713 subjects with NAFLD (M=269, F=444) were included. Mean age of subjects was 48.3 years; 61% had definite NASH, and 28% had bridging fibrosis or cirrhosis. Diabetes was present in 27% of subjects. Subjects with NAFLD had worse physical (mean=45.2) and mental health scores (mean=47.6) compared to the U.S. population with (mean=50) and without (physical: 55.8, mental: 52.5) chronic illness. Subjects with NASH reported lower physical health compared to subjects with fatty liver disease without NASH (44.5 vs. 47.1, p=.02). Subjects with cirrhosis had significantly (P<0.001) poorer physical health scores (38.4) vs. subjects with no (47.6), mild (46.2), moderate (44.6) or bridging fibrosis (44.6). Cirrhosis was associated with poorer physical health after adjusting for potential confounders.
Mental health scores did not differ between participants with and without NASH or by degree of fibrosis.

Adults with NAFLD have a significant decrement in QOL. Treatment of NAFLD should incorporate strategies to improve QOL, especially physical health.

1.2 Introduction

The increasing prevalence of obesity in North America has had significant effects on the prevalence of obesity-related conditions, including nonalcoholic fatty liver disease (NAFLD) (1). NAFLD is now the most common chronic liver disease in the United States (2,3). Epidemiological surveys estimate that 3% to 34% of the general population has NAFLD (2, 4-6) and that 2% to 5% have nonalcoholic steatohepatitis (NASH) (6-8).

Because of the increasing importance of NAFLD, many studies have focused on understanding the epidemiology, natural history, and associated comorbidities of NAFLD. Quality of life (QOL) has been less well evaluated in patients with NAFLD, but is a key element in assessing the burden of a disease and the personal impact of the disease on daily living. QOL measurement also allows for a common metric to compare the burden of different diseases. Previous studies of QOL in NAFLD have been characterized by mixed populations of liver disease with relatively small numbers of patients with NAFLD (9,10). The one study with a larger number of patients with NAFLD used solely a disease-specific, rather than generic, QOL measure (11). Notwithstanding the limitations, these previous studies suggest that NAFLD is associated with impaired QOL. Patients with multiple other forms of
chronic liver disease, including hepatitis C virus (HCV) (12), symptomatic hepatitis B virus (HBV) (13), and cholestatic liver disease (14), have also been shown to have decrements in QOL.

Using a large, multi-center sample, this study tested the hypothesis that individuals with NAFLD have lower QOL compared to individuals without NAFLD. QOL scores of individuals with NAFLD were compared to both a general reference U.S. population which included individuals with chronic illnesses, and to a healthy subset of the general population that excluded individuals with chronic illnesses. Because liver biopsies were available, a special focus of this study was the association between histologic severity of NAFLD and QOL in order to assess if increasing severity of disease was associated with lower QOL.

1.3 Methods

1.3.1 Subjects

The Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) was established by the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) in 2002 to assess the natural history, pathogenesis, and therapy of NAFLD in the United States (15). The baseline QOL data were obtained from adult subjects enrolled in two NASH CRN studies: (1) the NAFLD Database, an observational cohort study; and (2) a randomized, placebo-controlled clinical trial, PIVENS (Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis; Clinical Trial number NCT00063622). These studies were conducted by 8 Clinical Centers and a central Data Coordinating
Center. Both study protocols were approved by all participating center IRBs and an independent Data and Safety Monitoring Board. Each participant provided written informed consent.

1.3.2 Measures

1.3.2.1 Demographics

Demographic information collected during screening interviews as part of the registration process included age, gender, self-reported ethnic and racial affiliation, highest educational level achieved, marital status, employment status, and annual income.

1.3.2.2 Anthropometrics

Weight and height were measured with participants standing wearing light clothing. Body mass index (BMI) was calculated as the weight (kg) divided by the height (meters) squared. Weight status was defined as normal (BMI 18.5-24.9), overweight (BMI 25-29.9), mild obesity (BMI 30-34.9), moderate obesity (BMI 35-39.9), and severe obesity (BMI > 40).

1.3.2.3 Histology

The NASH CRN Pathology Committee developed and validated a feature-based histological scoring system that encompasses the spectrum of lesions of NAFLD (16). Liver biopsy slides from subjects were read centrally by the Pathology Committee during which biopsies were rigorously evaluated according to the
published scoring system (16). Steatosis was scored according to amount (%) of biopsy occupied using a four point scale. A diagnosis of NAFLD required the presence of $\geq 5\%$ steatosis. Fibrosis was staged from 0 to 4, with 0 = none; 1a = mild zone 3 (central) perisinusoidal fibrosis, 1b = moderate zone 3 perisinusoidal fibrosis, 1c = periportal and portal fibrosis (zone 1) only; 2 = both perisinusoidal and periportal or portal fibrosis; 3 = bridging fibrosis and 4 = cirrhosis. Diagnostic determinations of each biopsy were also assigned. Categories utilized were: definite steatohepatitis, definitely not steatohepatitis, borderline steatohepatitis (zone 3 pattern) and borderline steatohepatitis (zone 1 pattern).

1.3.2.4 Quality of life

The Short form 36 (SF-36) is a generic QOL assessment survey that is validated, widely used, and has shown good psychometric properties in diverse disease states including patients with advanced liver disease (17-21). The SF-36 consists of 36 questions that make up eight sub-scales (physical function, physical role limitation, bodily pain, general health, vitality, social function, emotional role limitation, and mental health). Within each dimension, 0 is the worst and 100 is the best possible score (22). An overall physical health score (physical component scale [PCS]) and mental health score (mental component scale [MCS]) are derived from the subscale scores. Norm-based scoring of the SF-36 was done according to the instructions provided in the SF-36 users manual (23). Norm-based scoring involves a linear transformation to transform scores to a mean of 50 and standard deviation of 10. Norm-based scoring results in a straightforward interpretation of the QOL scores; that
is, since the subscales have different ceilings and floors each score is affected by not only the disease being measured but also by arbitrary differences in the ceilings and floors of the particular scale. Therefore, familiarity with the mean of each scale is necessary when interpreting a particular scale score. With norm-based scoring, since each scale is scored to have a mean of 50 and the same standard deviation of 10, interpretation of a particular scale is clear-cut, greater than 50 equals better health than the U.S. population and less than 50 equals poorer health; additionally, one can easily see how many standard deviations a score is above or below the mean.

### 1.3.3 Data Analysis

Descriptive statistics (mean, median, percentiles, standard deviation, range) were used to characterize the sample population. A student’s t-test (continuous data) or chi-square test (categorical data) was used to compare characteristics between individuals with and without NASH. A student’s t-test was used to compare SF-36 scores between individuals with and without NASH. Univariable regression analyses were conducted to examine the unadjusted association between subjects’ characteristics and SF-36 scores. Multivariable regression analyses were conducted to identify factors independently associated with PCS and MCS SF-36 scores. Analysis of variance (ANOVA) was used to compare SF-36 scores by degree of fibrosis; Tukey’s post-hoc test was used to identify where specific differences, identified globally in the ANOVA, occurred. Dummy variables were created for categorical variables with more than two levels. For analyses age was categorized as 18-30 years, 31-40, 41-50, 51-60, and 61-76 years. Data were assessed, as appropriate, for meeting
regression assumptions prior to running analyses (i.e., linearity [assessed by partial regression plot], lack of multicollinearity [multicollinearity defined as Tolerance < .20 and/or Variance-inflation factor ≥4], homoscedasticity [assessed by simple regression plot], and absence of outliers [defined as standardized residuals greater than 3.3]). A p-value of <0.05 was considered statistically significant.

1.4 Results

1.4.1 Subjects’ Baseline Characteristics

There were 713 adults enrolled in the Database and/or PIVENS trial of the NASH CRN between October 27, 2004 and October 30, 2007 who had complete biopsy results available at the time of analysis, ≥ 5% steatosis, and complete QOL data. The mean age of the sample was 48 ± 12 years and 62% were female. The majority of participants were non-Hispanic White (76%), followed by Hispanic (13%), and non-Hispanic, non-White (8%). The majority of participants had some college education (71%), and one third had completed a bachelors degree or higher. More than half (58%) of the sample had a household income of at least $50,000 per year and 70% were currently employed. The majority of adults were married (69%). The mean BMI was 34.3 ± 6.5 Kg/m², 30% of subjects were mildly obese, 25% were moderately obese and 17% were severely obese. Type 2 diabetes was present in 27%. Sixty-one percent (436/713) had definite NASH, 20% (141/713) had borderline NASH, and 19% (136/713) had NAFLD but definitely not NASH. Twenty-three (167/713) percent had no fibrosis while 28% had bridging fibrosis or cirrhosis (197/713) (Table 1.1).
1.4.2 Baseline Characteristics, No NASH vs. NASH

There was a significantly (P = 0.006) greater proportion of females in the group with NASH (67%) than in those with NAFLD but without NASH (54%). Type 2 diabetes was more prevalent among adults with NASH than in those without NASH (32% vs. 19%, P = 0.005). There were no significant differences between adults with and without NASH in regards to age, race, marital status, employment status, or BMI (Table 1.1).

<table>
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<td>cirrhosis</td>
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*P-value is from comparison (t-test or Chi-Square test) between participants with definite NASH and participants with NAFLD but without NASH
1.4.3 Baseline QOL Scores

Individuals with NAFLD had significantly (P < 0.001) lower QOL for both physical (45.2) and mental health (47.6) than the general healthy U.S. population, (mean PCS score = 55.8, MCS score = 52.5). Individuals with NAFLD also had significantly (P < 0.001) lower QOL scores compared to the general U.S. population (including individuals with chronic illnesses; mean PCS and MCS scores = 50) (Figure 1.1). Age and gender adjustment of the U.S. normative sample did not change these results. All SF-36 subscale scores were also lower for adults with NAFLD compared to the U.S. general and healthy populations. Among adults with NAFLD, the lowest (worst) subscale mean scores were in general health (42.4), vitality (44.8), and physical functioning (45.6) (Figure 1.2).
Figure 1.1. Mean SF-36 PCS and MCS scores of adults enrolled in NASH CRN (n=713) and US normative sample with (n=1,982) and without (n=571) chronic illness. Error bars display standard deviations. Black bar = Mean scores of Individuals with NAFLD. Gray bar: Mean scores of general U.S. reference population. White bar with black diagonal lines: Mean scores of healthy (i.e., no chronic illness) reference sample. Mean PCS and MCS scores of NAFLD sample are significantly (P < 0.001) lower than PCS and MCS scores of general U.S. population and healthy sample.
Figure 1.2. Mean SF-36 sub-scale scores of adults enrolled in NASH CRN (n=713) and US normative sample with (n=1,982) and without (n=571) chronic illness. Error bars display standard deviations. Black bar = Mean scores of Individuals with NAFLD. Gray bar: Mean scores of general U.S. reference population. White bar with black diagonal lines: Mean scores of healthy (i.e., no chronic illness) reference sample. PF: Physical Function; RP: Role-Physical; RE: Role-Emotional; VT: Vitality; MH: Mental Health; SF: Social Function; BP: Bodily Pain; GH: General Health. Mean subscale scores of NAFLD sample are significantly (P ≤ 0.001) lower than subscales scores of general U.S. population and healthy sample.

1.4.4 Comparison of QOL Between Subjects With and Without NASH

Adults with definite NASH (PCS 44.5) reported significantly (P = 0.02) poorer physical health compared to adults with no NASH (PCS 47.1). For SF-36 subscale scores, adults with NASH reported significantly poorer vitality (44.3 vs. 46.6 for subjects with and without NASH, respectively, P = 0.04), general health (41.8 vs. 44.2 for subjects with and without NASH, respectively, P = 0.02), bodily pain (47.7 vs. 50.0 for subjects with and without NASH, respectively, P = 0.04) and role limitations
due to physical health (45.9 vs. 48.3 for subjects with and without NASH, respectively, $P = 0.04$). Individuals with and without NASH did not significantly differ in mental health (Table 1.2).

Table 1.2. QOL of Participants in the NASH CRN with and without NASH

<table>
<thead>
<tr>
<th>SF-36 PCS (standardized)</th>
<th>All subjects</th>
<th>NASH</th>
<th>No NASH</th>
<th>$P$-Value*</th>
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</thead>
<tbody>
<tr>
<td>N=713</td>
<td>N=436</td>
<td>N=136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± sd (range)</td>
<td>45.2 ± 10.9 (15.7 - 63.8)</td>
<td>44.5 ± 11.0</td>
<td>47.1 ± 10.4</td>
<td>0.018</td>
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<table>
<thead>
<tr>
<th>SF-36 MCS (standardized)</th>
<th>All subjects</th>
<th>NASH</th>
<th>No NASH</th>
<th>$P$-Value*</th>
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</thead>
<tbody>
<tr>
<td>N=713</td>
<td>N=436</td>
<td>N=136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± sd (range)</td>
<td>47.6 ± 11.0 (9.2 – 68.7)</td>
<td>47.5 ± 10.9</td>
<td>48.6 ± 11.3</td>
<td>0.342</td>
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</table>

<table>
<thead>
<tr>
<th>SF-36 Sub-Scales (standardized)</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>$P$-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>45.6 ± 11.3</td>
<td>44.9 ± 11.7</td>
<td>47.0 ± 11.0</td>
<td>0.066</td>
</tr>
<tr>
<td>Role limitations due to physical health</td>
<td>46.5 ± 11.6</td>
<td>45.8 ± 11.6</td>
<td>48.3 ± 11.4</td>
<td>0.036</td>
</tr>
<tr>
<td>Role limitations due to emotional problems</td>
<td>47.1 ± 12.2</td>
<td>46.9 ± 12.1</td>
<td>48.6 ± 12.0</td>
<td>0.154</td>
</tr>
<tr>
<td>Vitality</td>
<td>44.8 ± 11.2</td>
<td>44.4 ± 11.1</td>
<td>46.6 ± 11.5</td>
<td>0.043</td>
</tr>
<tr>
<td>Mental Health</td>
<td>48.3 ± 10.8</td>
<td>48.0 ± 10.7</td>
<td>49.1 ± 11.7</td>
<td>0.336</td>
</tr>
<tr>
<td>Social functioning</td>
<td>46.9 ± 11.6</td>
<td>46.9 ± 11.3</td>
<td>48.0 ± 12.0</td>
<td>0.328</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>48.0 ± 11.2</td>
<td>47.7 ± 11.2</td>
<td>50.0 ± 11.4</td>
<td>0.043</td>
</tr>
<tr>
<td>General Health</td>
<td>42.4 ± 10.8</td>
<td>41.8 ± 10.9</td>
<td>44.2 ± 10.9</td>
<td>0.023</td>
</tr>
</tbody>
</table>

*P-value is from comparison (t-test) between participants with definite NASH and participants with NAFLD but without NASH.
1.4.5 Factors Associated With QOL in Subjects With NAFLD

In univariable analyses, the following characteristics were significantly (P < 0.05) associated with poorer physical health: age greater than 40 years, female gender, type 2 diabetes, whether or not there NASH was present, income less than $15,000, divorced, separated or widowed marital status, and BMI of ≥ 40. Race and level of education were not associated with physical health score.

In multivariable analysis, characteristics significantly associated with poorer physical health, after adjusting for all other variables in the model, included: older age (vs. age 18-30 yrs. age 41-50 yrs., B: -3.34, P = 0.031; age 51-60 yrs., B: -4.69, P = 0.003; age 61-76 yrs., B: -4.85, P = 0.004), female gender (B: -4.67, P < 0.001), type 2 diabetes (B: -4.11, P < 0.001), and lower income ($30K-49.4K vs. <$15,000, B: 4.65, P = 0.002; ≥50K vs. <$15,000, B: 7.24, P < 0.001). The presence of NASH as determined by liver histology was not independently associated with poorer physical health.

Characteristics significantly (P < 0.05) associated with poorer mental health in univariate analysis included: female gender, type 2 diabetes, income of less than $15,000, less than high school diploma, and divorced, separated or widowed marital status. Age, presence of NASH, race, and BMI were not associated with mental health score.

In multivariable analysis, characteristics significantly associated with poorer mental health, after adjusting for all other variables in the model, included: female gender (B: -2.40, P = 0.007), age 18-30 yrs (vs. 61-76 yrs., B: -4.91, P = 0.010), type 2
diabetes (B: -2.12, p=0.028), less than high school diploma (B: -3.94, P = 0.020), and annual household lower income (≥ $50K vs. <15,000, B: 5.36, P = 0.001).

1.4.6 Gender Stratified Multivariable Analyses

Since gender was a significant independent predictor of both MCS and PCS, multivariable models were re-run stratified by gender. Older age, type 2 diabetes and low household income were associated with poorer physical health in both men and women. Divorced, separated or widowed marital status (vs. married) was associated with worse mental health in men; low household income and less than high school diploma were associated with worse mental health in women.

1.4.7 QOL by Degree of Fibrosis

As shown in Figure 1.3, there was a significant (P < 0.001) overall difference in physical health score between the fibrosis groups; scores tended to worsen as the amount of fibrosis increased. Tukey's multiple comparison tests demonstrated that participants with cirrhosis reported significantly worse physical health compared to each of the other groups (all P-values ≤ 0.001). After adjusting for age, gender, race, marital status, education, annual household income, BMI, and type 2 diabetes, presence of cirrhosis was independently associated with significantly worse physical health score compared to no fibrosis (B= -5.06, P < 0.001). The difference in mental health scores did not significantly differ between the fibrosis categories.
Figure 1.3. Median PCS scores and interquartile range by degree of fibrosis. ANOVA and Tukey’s post-hoc analysis demonstrated that PCS score for individuals with cirrhosis was significantly (P < 0.001) lower than each of the other groups.

1.5 Discussion

These data demonstrate that individuals with the full spectrum of NAFLD have reduced QOL. Impairment in QOL is most evident in physical health while mental health is affected to a lesser degree. Furthermore, there was an inverse relationship between severity of NAFLD and lower QOL, and increased fibrosis portended a decrease in physical QOL. Factors independently associated with lower QOL included older age, female gender, presence of type 2 diabetes, and poverty.

QOL was particularly low in individuals with cirrhosis; after adjustment for other characteristics cirrhosis remained a significant independent predictor of lower physical health score. Previous studies have reported lower QOL in cirrhotic patients
compared to normal controls and liver disease patients without cirrhosis. However, the majority of those studies were limited by small sample sizes (19,24,25), use of single center samples (13, 26-30), disease-specific measures (31,32), and/or the inclusion of univariable analysis only (9, 26-28, 33). Studies that have utilized surrogate measures of cirrhosis, i.e., presence of splenomegaly or patient self-report of cirrhosis, suggested that cirrhosis may be independently associated with lower QOL, in a variety of other liver diseases (34,35). In this study there was a strong association between presence of cirrhosis and lower QOL in individuals with NAFLD.

Subjects with NAFLD reported physical QOL scores that were an average of 4.9 points lower than the general U.S. reference population while mental health scores were on average 2.4 points lower. The reference population includes individuals with chronic diseases, possibly including NAFLD - 22% of the sample reported presence of type 2 diabetes and 27% reported hypertension, two conditions associated with NAFLD. Comparing the NAFLD sample to a sub-set of the reference population that excluded individuals with chronic disease (23), the physical scores of the NAFLD sample were an average of 10.7 points lower, and mental health scores were an average of 4.9 points lower. Discussions surrounding what constitutes a clinically significant difference in QOL scores are longstanding (36). A difference in scores of at least half of a standard deviation (i.e., 5 points) is generally believed to be a conservative estimate of a clinically significant effect size (37). In this study, physical health scores were a half standard deviation lower than the U.S. general population and a full standard deviation lower than individuals without chronic health conditions. Conversely, the mental health scores of individuals with NAFLD are likely clinically
significantly lower than individuals without chronic health conditions, but not significantly different than the U.S. general population.

Although QOL is a relatively new concept to the study of NAFLD, QOL research itself is not new. Standard methods in QOL research are to detect if QOL differences exist, and, if so, to then identify what factors underlie the difference. By identifying and intervening on modifiable factors that are found to be associated with decreased QOL, improvements in QOL can be realized. While NAFLD is generally asymptomatic, fatigue is one symptom shown to be common in individuals with NAFLD (38), and to negatively affect QOL of individuals with other types of liver disease (9, 24, 39-42). Thus, NAFLD-associated symptoms, in particular fatigue, may contribute to decreased QOL. A recent study demonstrated that fatigue was significantly associated with a decrease in all domains of the Chronic Liver Disease Questionnaire in individuals with NAFLD (11). In the present study, vitality was one of the QOL dimensions on which individuals with NAFLD reported the lowest scores.

The current data suggest that individuals with NAFLD have a greater degree of limitation in physical health than patients with other types of liver disease. Using a liver disease-specific instrument, patients with NAFLD reported greater systemic symptoms and greater degrees of limitations in activity compared to patients with HBV or HCV (11). It is notable that the PCS scores of individuals with NAFLD in this study are comparable to the PCS scores reported for patients with HBV who had decompensated cirrhosis (13). From the studies done to date it is unknown whether poor physical function contributes to NAFLD and NAFLD severity, or conversely, if presence of NAFLD results in poor physical function.
Obesity (43-46) and diabetes (23) are two common co-morbidities in individuals with NAFLD (41), and are also associated with decreased QOL. Moreover, the presence of co-morbid illness has been associated with decreased QOL in patients with other chronic liver diseases (47,48). In the current study, patients with severe obesity had significantly lower QOL than patients who were normal weight, although there was not an independent relationship between BMI and QOL score after adjustment for other covariates. Conversely, the presence of type 2 diabetes had a significant independent negative association with both physical and mental QOL scores. However, cirrhosis was associated with lower QOL physical health score after adjusting for presence of type 2 diabetes. Thus, type 2 diabetes does not fully explain the decreased QOL in NAFLD.

Assessment of QOL is useful because this measure provides information about the overall burden of NAFLD from the individual’s perspective. In addition to the negative impact poor physical health may have on an individual personally, there may be other important implications of poor self-reported physical health. A recent study found that NAFLD is associated with significant increases in medical costs and health care utilization over time (49). The degree that health perception influences health care seeking behavior is unknown but it can be hypothesized that poor physical health perception may impact health care utilization in individuals with NAFLD. Productivity may also be affected by poor physical health perception. One study found that lower SF-36 physical health score significantly differentiated between individuals who returned to work following liver transplantation and those who did not, despite the fact that all participants reported good health status as measured by a performance
status scale (50). Poor QOL also has implications for mortality. In numerous studies, including those in patients with a variety of chronic and acute disease states, (e.g., type 2 diabetes (51), arthritis (52), COPD (53), hemodialysis patients (54)) low QOL scores have been associated with increased mortality risk (55). Thus, poor subjective physical health has important implications in terms of increased health care utilization, productivity losses, and mortality.

The multi-center design of the NASH CRN and the recruitment of subjects from a variety of settings make these results generalizable to adults in the U.S. with a clinical diagnosis of NAFLD. An additional strength of this study was the inclusion of liver histology on all patients with a rigorous, standardized, central biopsy review. A limitation was the cross sectional nature of the study, thus we cannot determine cause and effect from these data. Longitudinal studies of NAFLD are warranted to clarify the nature and direction of associations identified from cross sectional data.

In summary, individuals with NAFLD have lower QOL than the U.S. general population, with and without chronic illness. Decrement in physical health is particularly apparent. Future research should focus on identifying modifiable factors that affect QOL and can be targeted for improvement. The independent inverse relationship between cirrhosis and physical health is novel and merits further evaluation. The association between diabetes and NAFLD severity, and between diabetes and QOL in adults with NAFLD warrants additional attention as these patients will increasingly be co-managed by internists, endocrinologists, and hepatologists.
1.6 Acknowledgements

Chapter 1, in part, was presented as a poster at AASLD, in San Francisco, CA on November 2, 2008. The dissertation author was the first author of this poster: Kristin David, Aynur Unalp, Fasiha Kanwal, Kris V. Kowdley, Jeffrey B. Schwimmer, and the NASH CRN Research Group: “Health related quality of life in adults with nonalcoholic fatty liver disease: Baseline data from the NASH CRN.” Abstract #1120. Hepatology, 2008;48:4 (SUPPL):807A

Chapter 1 has been submitted for publication of the material as it may appear in Hepatology, 2009. The dissertation author was the first author of this paper: Kristin D. Kistler, Aynur Unalp, Fasiha Kanwal, Kris V. Kowdley, Jeffrey B. Schwimmer, and the NASH CRN Research Group. Health related quality of life in adults with nonalcoholic fatty liver disease: Baseline data from the NASH CRN. Submitted to Hepatology.
1.7 Chapter 1 References


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Chapter 2: Symptoms and Quality of Life in Children with Nonalcoholic Fatty Liver Disease

2.1 Abstract

Nonalcoholic fatty liver disease (NAFLD) is a common cause of liver disease in children. Data on the quality of life (QOL) of children with NAFLD are needed to estimate the true burden of illness in children with NAFLD.

The aim was to characterize QOL and symptoms of children with NAFLD, and to compare QOL in children with NAFLD to a reference sample of healthy children.

QOL and symptoms were assessed in children with biopsy-proven NAFLD enrolled in the NASH Clinical Research Network. PedsQL scores were compared to scores from healthy children. For children with NAFLD, between groups comparisons were made to test associations of demography, histologic severity, symptoms and QOL.

Two-hundred thirty-nine children with a mean age of 12.6 years were analyzed. Children with NAFLD had worse total health (72.8 vs. 83.8, p<.01), physical health (77.2 vs. 87.5, p<.01) and psychosocial health (70.4 vs. 81.9, p<.01) scores compared to healthy children. Irritability, fatigue, headache, trouble concentrating, and muscle aches were frequent symptoms. QOL scores did not significantly differ by the presence of steatohepatitis or degree of fibrosis. Fatigue, trouble sleeping, and sadness accounted for almost half of the variance in QOL scores. Impaired QOL was present in 39% of children with NAFLD.
Children with NAFLD have a decrement in QOL relative to healthy children. Symptoms, particularly fatigue, were a major determinant of this impairment. Future studies must delineate the mechanism of decreased QOL and develop interventions to restore and optimize QOL in children with NAFLD.

2.2 Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in children (1) and is an important risk factor for future diabetes and cardiovascular disease. (2) NAFLD is defined by macrovesicular steatosis in \( \geq 5\% \) of hepatocytes with little or no exposure to alcohol and the exclusion of other types of liver disease. The spectrum of NAFLD ranges from isolated steatosis to steatohepatitis (nonalcoholic steatohepatitis [NASH]), with progressive injury including fibrosis, cirrhosis, liver failure and hepatocellular carcinoma. (3,4) The high prevalence of NAFLD and its risk for future morbidity have resulted in the recognition of NAFLD as an important disease entity in children. (5-8) While the hepatic, cardiovascular, and endocrine effects of NAFLD are evident, (9) NAFLD may also be associated with effects on quality of life (QOL).

QOL measurement is an important component to the complete understanding of disease burden. QOL is a subjective measure of a disease’s overall impact from an individual’s perspective. Traditional indicators of disease burden such as mortality and objective measures of morbidity may underestimate the impact of disease on an individual. This may be particularly true in the case of chronic diseases. Symptoms have the potential for direct effects on QOL. However, the full range of symptoms in
children with NAFLD is not well characterized. In some cases, NAFLD may be associated with symptoms such as abdominal pain or fatigue. Recent data demonstrate that fatigue is highly prevalent in adults with NAFLD, (10) and fatigue is independently associated with lower QOL in adults with other types of chronic liver disease. (11) In addition to the potential for symptoms to directly effect QOL, indirect effects such as the emotional influence of worrying about one’s disease may also decrease QOL. Emotional effects of chronic illnesses are often greater than physical effects on the QOL of children (12,13) and are only quantifiable using a QOL measure. Thus, QOL measurement provides information on disease-related burden of illness that may otherwise be missed if relying solely on standard clinical measures.

The aim of this study was to describe the QOL of children with NAFLD. In order to place the findings in a meaningful context, we compared the QOL of children with NAFLD to a reference sample of healthy children. A secondary aim was to characterize the range and severity of symptoms in children with NAFLD, and to evaluate whether symptoms and NAFLD severity were predictors of QOL. Using baseline data from a large, multi center sample of NAFLD, the NASH CRN, we included a broadly representative sample that encompassed the full range of NAFLD.

2.3 Methods

2.3.1 Subjects

The Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) was established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in 2002 to assess the natural history, pathogenesis, and therapy of
NAFLD in both children and adults in the United States.(14,15) Data in this paper come from two NASH CRN studies: (1) the NAFLD Database, an observational cohort study, and (2) a randomized, placebo-controlled pediatric treatment trial entitled ‘Treatment of Nonalcoholic Fatty Liver Disease in Children’ (TONIC) (Clinical Trial #NCT00063635). These studies are conducted by 8 Clinical Centers and a central Data Coordinating Center of the NASH CRN. Both study protocols were approved by all participating center institutional review boards and an independent Data and Safety Monitoring Board.

The participant selection criteria for inclusion in the NASH CRN have been previously reported.(16) Inclusion criteria for the present analysis were age 5-17 years and biopsy-proven NAFLD. Participants with < 5% steatosis or missing histology or QOL data were excluded.

2.3.2 Measures

2.3.2.1 Demographics

Demographic information was collected during screening interviews as part of the registration process, including age, gender, self-reported race and ethnicity, and family annual income.

2.3.2.2 Anthropometrics

Height and weight (without shoes or heavy clothing) were measured at the participants initial study visit. Body Mass Index (BMI) was calculated as weight (kg) / [height (m)]². BMI z-scores and percentiles were calculated using data provided on
the CDC web site. Specifically, the following parameters were obtained: the median (M), the generalized coefficient of variation (S), and the power in the Box-Cox transformation (L). To obtain the z-score (Z) and corresponding percentile for a given BMI, the following equation was used: \( Z = \frac{\ln(\text{BMI}/M)}{S}, \text{L}=0 \). Obesity was defined as a BMI above the age- and gender-specific 95th percentile cutoff points from the 2000 CDC BMI Charts. Overweight was defined as BMI between the 85th and 95th percentiles.

2.3.2.3 Histology

The NASH CRN Pathology Committee developed and validated a feature-based histological scoring system that encompasses the spectrum of lesions of NAFLD. Liver biopsy slides from subjects were read centrally by the Pathology Committee during which biopsies were rigorously evaluated according to the published scoring system. Steatosis was scored according to the percentage of hepatocytes containing fat droplets. A diagnosis of NAFLD required the presence of \( \geq 5\% \) steatosis. Fibrosis was staged as follows: 1a and 1b are zone 3 perisinusoidal fibrosis, mild (requiring trichrome stain) and moderate, visible on H&E stained slides, respectively. Stage 1c is portal fibrosis only. Stage 2 is zone 3 perisinusoidal plus periportal fibrosis. Stage 3 is bridging fibrosis and 4 is definite or probable cirrhosis. Each biopsy was classified into one of the following diagnostic categories: definite steatohepatitis, not steatohepatitis, borderline steatohepatitis (zone 3 pattern) and borderline steatohepatitis (zone 1 pattern).
2.3.2.4 Quality of life

The PedsQL 4.0 (Pediatric Quality of Life Inventory™ Version 4.0) is a general quality of life measure comprised of 23 items that make up 4 core scales: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items).(19,20) The PedsQL uses a 5-point likert scale (0=never a problem; 4=almost always a problem). Items are reverse-scored and linearly transformed to a zero to 100 scale (0=100, 1=75, 2=50, 3=25, 4=0), so that higher scores indicate better health-related QOL. A total QOL score (derived by the mean of all 23 items), a physical health summary score (mean of items in the physical health subscale) and a psychosocial health summary score (mean of items in the emotional, social, and school functioning subscales) are calculated to provide a summary of the child or adolescent’s health-related QOL. Children with NAFLD were also categorized as having impaired QOL and not impaired QOL in order to examine whether there were different demographic and/or clinical factors that characterized children with impaired QOL. The PedsQL was self-administered for parents and for children ages 8 to 17 and interview administered for children ages 5 to 7, in their preferred language (Spanish or English).

2.3.2.5 Symptoms, Frequency and Severity

Participants self-reported the presence of the following symptoms using the NIDDK Symptoms of Liver Disease questionnaire: Neuropsychological: fatigue, irritability, sadness, trouble concentrating, and trouble sleeping; Physical: diarrhea, nausea, swelling of abdomen, swelling of ankles; and Pain: headache, liver pain,
muscle aches/cramps. Participants reported whether they were bothered by the symptom in the past month: not at all (none), a little bit (mild), medium (moderate), quite a bit or extremely (severe).

2.3.3 Data analysis

Descriptive statistics (mean, median, standard deviation, frequencies, and percentages) were used to characterize the sample population. A student’s t-test (continuous data) or chi-square test (categorical data) was used to compare characteristics between boys and girls. A student’s t-test was used to compare PedsQL scores between boys and girls and between the NASH CRN sample and a reference sample of healthy children (20) reported in the literature. The healthy reference sample included slightly more boys than girls and had a similar age range (5 to 18) and ethnic distribution (Hispanic 62%) as the NASH CRN sample. Analysis of variance (ANOVA) was used to compare PedsQL scores by degree of fibrosis. Multiple regression analysis was conducted to identify factors independently associated with PedsQL score. Factors included in the multiple regression models were: gender, age (<10 years, 10-13 years, and 14-17 years), race (non-Hispanic White, Non-Hispanic, non-White or non-Hispanic, multi-ethnic, and Hispanic), BMI z-score, and presence of each symptom (yes/no). Dummy variables were created for categorical variables with more than two levels. In all multiple regression models, multicollinearity among variables was assessed by examining Tolerance and Variance-inflation factor values (multicollinearity defined as Tolerance < .20 and/or Variance-inflation factor ≥4). Homoscedasticity was assessed by simple regression plots, and
outliers were assessed by examining standardized residuals [outlier defined as standardized residuals greater than 3.3). A p-value of <.05 was considered statistically significant.

To examine determinants of impaired QOL, children who met the definition of impaired QOL were compared to children who did not have impaired QOL. Impaired QOL was defined as being 1 or more standard deviations below the mean total QOL score of the healthy reference population (i.e., a score of less than or equal to 71.2).(21) QOL was quantified as not impaired if the total QOL score was equal to or above the mean total QOL score of the healthy reference population (i.e., a score of equal to or greater than 83.8).

2.4 Results

2.4.1 Participants’ Baseline Characteristics

There were 331 children enrolled in the NASH CRN as of May 2007, of these 239 met inclusion and exclusion criteria and were included in this analysis (Table 2.1). The mean age of participants was 12.6 ± 2.5 years. Consistent with the epidemiology of pediatric NAFLD, there were more boys than girls.(1,22) Also consistent with the epidemiology of pediatric NAFLD, the majority of participants were Hispanic (62%) followed by non-Hispanic White (31%), and non-Hispanic, non-White (7%). The mean BMI of participants was 32.8 ± 5.6 Kg/m2. Four percent (n=9) had type 2 diabetes. Thirty-nine percent (n=94) had definite NASH, 38% (n=91) had borderline NASH (n=55 zone 1 pattern; n=36 zone 3 pattern), and 23% (n=54) had NAFLD but
not NASH. There were no significant differences between boys and girls for presence of NASH or fibrosis (Table 2.1).

**Table 2.1. Baseline Characteristics of Children Enrolled in the NASH CRN**

<table>
<thead>
<tr>
<th></th>
<th>Total (N=239)</th>
<th>Boys (N=174)</th>
<th>Girls (N=65)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs.)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>12.56 ± 2.46</td>
<td>12.60 ± 2.36</td>
<td>12.45 ± 2.74</td>
<td>0.683</td>
</tr>
<tr>
<td><strong>Age Category</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 yrs.</td>
<td>24 (10.0%)</td>
<td>14 (8.0%)</td>
<td>10 (15.4%)</td>
<td>0.089</td>
</tr>
<tr>
<td>10 –13 yrs.</td>
<td>131 (54.8%)</td>
<td>102 (58.6%)</td>
<td>29 (44.6%)</td>
<td></td>
</tr>
<tr>
<td>14 – 17 yrs.</td>
<td>84 (35.1%)</td>
<td>58 (33.3%)</td>
<td>26 (40.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>148 (61.9%)</td>
<td>106 (60.9%)</td>
<td>42 (64.6%)</td>
<td></td>
</tr>
<tr>
<td>White, Non-Hispanic</td>
<td>75 (31.5%)</td>
<td>59 (33.3%)</td>
<td>16 (24.6%)</td>
<td>0.229</td>
</tr>
<tr>
<td>Non-White, Non-Hispanic¹</td>
<td>16 (6.7%)</td>
<td>9 (5.7%)</td>
<td>7 (10.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Weight (kg.)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>85.63 ± 23.30</td>
<td>87.43 ± 22.99</td>
<td>81.75 ± 25.35</td>
<td>0.050</td>
</tr>
<tr>
<td><strong>Height (m)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.60 ± .140</td>
<td>1.62 ± .142</td>
<td>1.56 ± .115</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>32.77 ± 5.57</td>
<td>32.75 ± 5.22</td>
<td>33.00 ± 6.85</td>
<td>0.945</td>
</tr>
<tr>
<td><strong>BMI z-score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.32 ± .350</td>
<td>2.35 ± .345</td>
<td>2.24 ± .369</td>
<td>0.055</td>
</tr>
<tr>
<td><strong>BMI percentile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>98.50 ± 1.73</td>
<td>98.60 ± 1.77</td>
<td>98.18 ± 1.76</td>
<td>0.160</td>
</tr>
</tbody>
</table>
Table 2.1. Baseline Characteristics of Children Enrolled in the NASH CRN

continued

<table>
<thead>
<tr>
<th>BMI percentile category</th>
<th>Total (N=239)</th>
<th>Boys (N=174)</th>
<th>Girls (N=65)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight (85th - &lt;95th %)</td>
<td>10 (4.2%)</td>
<td>7 (4.0%)</td>
<td>3 (4.6%)</td>
<td>0.545</td>
</tr>
<tr>
<td>Obese (&gt;=95th %)</td>
<td>228 (95.0%)</td>
<td>166 (96.0%)</td>
<td>62 (95.4%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 2 Diabetes</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>9 (3.8%)</td>
<td>2 (1.1%)</td>
<td>7 (10.8%)</td>
<td>0.002</td>
</tr>
<tr>
<td>No</td>
<td>230 (96.2%)</td>
<td>172 (98.9%)</td>
<td>58 (89.2%)</td>
<td></td>
</tr>
</tbody>
</table>

1 Category includes 4 multi-racial subjects (non-Hispanic), and 1 subject missing race

2.4.2 NAFLD-Associated Symptoms

Figure 2.1 shows the frequency and severity of reported symptoms. The presence of multiple symptoms was common, with 50% of participants reporting having 5 or more symptoms. Irritability was the most common individual symptom (reported by 73% of children). Other common symptoms were fatigue (68%), headache (60%), trouble concentrating (55%), and muscle aches or cramps (53%). The other symptoms were reported as being present by less than half of the children. In addition to being the most frequently reported symptom, irritability was the most severe symptom, with 65 of 239 children (27%) reporting severe irritability. Other symptoms frequently rated as severe were trouble concentrating (21%) and fatigue (17%).
2.4.3 QOL of Children with NAFLD versus Healthy Children

The mean total QOL score for children with NAFLD was $72.7 \pm 15.5$ (Table 2.2). There were no significant differences in QOL between participants with definite NASH, borderline NASH, and NAFLD but definitely not NASH, $p=0.49$. Similarly, there were no significant differences in QOL by degree of fibrosis (none, 1a-zone 3, bridging/fibrosis), $p=0.71$. 

Figure 2.1. Frequency and severity of symptoms in children with NAFLD
As shown in Table 2.2, children with NAFLD reported significantly (p<0.01) lower QOL (72.7) compared to healthy children (83.8). Physical health and psychosocial health were also significantly (p<0.01) lower for children with NAFLD. The greatest discrepancy in scores between children with NAFLD and healthy children was in psychosocial health. The largest contributor to poor psychosocial health in children with NAFLD was school functioning.

Consistent with studies of children with chronic diseases,(20) parent proxy scores were significantly lower than the child self-reported QOL scores (e.g., NAFLD parent proxy report mean total QOL score: 64.8 ± 18.0, p<0.01). Parents’ proxy reports of QOL of children with NAFLD were also significantly (p<0.001) lower than the proxy reports of parents of healthy children (Table 2.2).

Table 2.2. Comparison of QOL Scores between Children with NAFLD and Healthy Children

<table>
<thead>
<tr>
<th></th>
<th>Parents of NAFLD</th>
<th>Parents of Healthy Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-report</strong></td>
<td><strong>Healthy</strong></td>
<td><strong>Children</strong></td>
</tr>
<tr>
<td>NAFLD</td>
<td>N=240</td>
<td>N=5480</td>
</tr>
<tr>
<td>Physical Health Score</td>
<td>77.1 (17.6)</td>
<td>87.5 (13.5)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Proxy Report</strong></td>
<td><strong>Proxy Report</strong></td>
<td></td>
</tr>
<tr>
<td>NAFLD</td>
<td>N=240</td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>72.7 (15.5)</td>
<td>83.8 (12.7)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical Health Score</td>
<td>77.1 (17.6)</td>
<td>87.5 (13.5)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 2.2. Comparison of QOL Scores between Children with NAFLD and Healthy Children continued

<table>
<thead>
<tr>
<th></th>
<th>Parents of NAFLD</th>
<th>Parents of Healthy Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAFLD</td>
<td>N=240</td>
<td>N=5480</td>
</tr>
<tr>
<td>Healthy Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>70.3 (16.7)</td>
<td>81.9 (14.1)</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>68.5 (20.6)</td>
<td>79.3 (18.2)</td>
</tr>
<tr>
<td>School Functioning</td>
<td>77.0 (20.8)</td>
<td>81.1 (16.8)</td>
</tr>
<tr>
<td>Psychosocial health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>65.4 (19.7)</td>
<td>81.1 (16.5)</td>
</tr>
</tbody>
</table>

1Comparison is between children with NAFLD and Healthy Children; Healthy reference sample from (20)

2Comparison is between parent proxy report of children with NAFLD and parent proxy report of healthy children. (20)

2.4.4 Comparison of QOL between Boys and Girls with NAFLD

Boys reported significantly (p<0.05) higher total QOL (74.0) than girls (69.6). The difference in total QOL was primarily due to the large difference in physical health for boys (79.0) compared to girls (72.6), p=0.001. Psychosocial health scores did not significantly differ between boys and girls (Table 2.3).
Table 2.3. QOL Scores Stratified by Sex

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th>Girls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>74.0 (16.1)</td>
<td>69.0 (12.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Physical health score</td>
<td>79.1 (17.7)</td>
<td>71.9 (16.4)</td>
<td>0.005</td>
</tr>
<tr>
<td>Psychosocial health score</td>
<td>71.4 (17.5)</td>
<td>67.5 (14.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>69.9 (20.8)</td>
<td>64.6 (19.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>77.6 (21.6)</td>
<td>75.3 (18.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>School Functioning</td>
<td>66.6 (19.8)</td>
<td>62.5 (19.2)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

2.4.5 Factors Associated with QOL in Participants with NAFLD

A multiple regression model assessed the association between demography, histology, obesity, and symptoms with QOL in children with NAFLD. Symptoms were the only factors independently associated with overall QOL, as well as for the subscales of physical and psychosocial health. Symptoms significantly associated with lower QOL included: fatigue (p=0.030), sadness (p=0.002), and trouble sleeping (p=0.010) (model $R^2 = 0.45$). Fatigue (p=0.026), sadness (p=0.027), and trouble sleeping (p=0.017) were also significantly associated with lower physical health (model $R^2 = 0.29$). Lower psychosocial health was associated with sadness (p=0.002), trouble sleeping (p=0.029), nausea (p=0.005), diarrhea (p=0.025), muscle aches or cramps (p=0.016), and trouble concentrating (p=0.037) (model $R^2 = 0.47$). Based upon the presence or absence of each symptom, the 3 symptoms that had the strongest association with QOL were fatigue, trouble sleeping, and sadness. Therefore we
examined the relationship between the severity of each of these symptoms and QOL. As shown in Figure 2.2, there was a significant (p < 0.01) inverse relationship between symptom severity and overall QOL.

Impaired QOL was noted in 39% of children. Children with impaired QOL had a mean QOL score of 57.6 ± 12.3. Impaired QOL was significantly (p<.001) more frequent in girls (35/65, 54%) than boys (58/175, 33%). Children of non-Hispanic ethnicity were significantly (p=0.002) more likely to have impaired QOL (36/75, 48%) than Hispanic children (47/148, 32%). Impaired QOL was not significantly (p>0.05) associated with BMI z-score, age, presence of NASH, or stage of fibrosis. As shown in Table 2.4, children who had impaired QOL were significantly (p<.05) more likely to report most symptoms than children without impaired QOL. Impaired QOL, after adjustment for sex, race, BMI z-score, and each symptom, had a significant independent association with 3 symptoms: fatigue (β = -0.18, p=0.02), trouble concentrating (β = -0.20, p=.013), and nausea (β = -0.22, p=.03).
Figure 2.2. Total QOL score by severity of (A) sadness, (B) fatigue, and (C) trouble sleeping. ANOVA demonstrated significant (p<0.001) overall differences for each symptom. Tukey’s post-hoc test demonstrated that: * significantly (p<0.01) different from category none; † significantly (p≤0.01) different from category mild. Boxes=median scores; whiskers=interquartile range
Table 2.4: Baseline Characteristics of Children Enrolled in the NASH CRN with Impaired Versus Not Impaired QOL

<table>
<thead>
<tr>
<th>Symptom (present)</th>
<th>Total N=239</th>
<th>Impaired QOL N=93</th>
<th>Not Impaired QOL N=50</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropsychological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>163 (67.9%)</td>
<td>83 (89.2%)</td>
<td>18 (36.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Irritability</td>
<td>174 (72.5%)</td>
<td>79 (84.9%)</td>
<td>24 (48.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sadness</td>
<td>112 (46.7%)</td>
<td>65 (69.9%)</td>
<td>4 (8.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trouble concentrating</td>
<td>132 (55.0%)</td>
<td>68 (73.1%)</td>
<td>11 (22.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trouble sleeping</td>
<td>118 (49.2%)</td>
<td>64 (68.8%)</td>
<td>9 (18.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Physical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>85 (35.4%)</td>
<td>50 (53.8%)</td>
<td>5 (10.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>117 (48.8%)</td>
<td>65 (69.9%)</td>
<td>12 (24.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Swelling abdomen</td>
<td>49 (20.4%)</td>
<td>29 (31.2%)</td>
<td>7 (14.0%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Swelling ankles</td>
<td>36 (15.0%)</td>
<td>23 (24.7%)</td>
<td>6 (12.0%)</td>
<td>0.083</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>143 (59.6%)</td>
<td>66 (71.0%)</td>
<td>16 (32.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver pain</td>
<td>99 (41.3%)</td>
<td>55 (59.1%)</td>
<td>9 (18.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Muscle aches/cramps</td>
<td>126 (52.5%)</td>
<td>64 (68.8%)</td>
<td>17 (34.0%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

2.5 Discussion

In a large, multi-center study, children with biopsy-proven NAFLD reported lower QOL scores than a reference sample of healthy children. Furthermore, nearly
40% of children with NAFLD had impaired QOL. Among children with NAFLD, QOL did not differ by histological severity of disease. There was a high rate of symptoms reported by children with NAFLD. The symptoms of fatigue, trouble sleeping, and sadness accounted for almost half of the variance in QOL scores in children with NAFLD. In addition, fatigue, along with trouble concentrating and nausea, were independently associated with impaired QOL.

Assessment of QOL is useful because this measure provides information about the overall burden of NAFLD from the individual’s perspective. The current data advance the understanding of QOL in children with NAFLD, yet further studies are needed to understand the mechanism of reduced QOL experienced by children with NAFLD. The QOL scores reported by children with NAFLD were comparable with the range of scores reported by children with other chronic diseases (e.g. asthma: 74.9 (20), type 2 diabetes: 76.7 (23)). Beyond NAFLD, the study of QOL in pediatric liver disease is relatively nascent. The majority of studies have focused on QOL after liver transplantation,(24-28) and have demonstrated impaired QOL compared to healthy reference groups. Two studies have reported QOL data on children with chronic hepatitis C. One demonstrated a decrease in QOL only during treatment with alpha interferon,(29) and the other small study of 19 children with hepatitis C demonstrated impaired QOL compared to normal controls.(30) In a pilot study of children with NASH, Schwimmer et al.(31) showed significant impairment in QOL prior to treatment with metformin. These limited studies, using different instruments, demonstrate marked impairment of QOL in children following liver transplantation,
moderate impairment in children with NASH, and inconsistent findings for children
with hepatitis C.

NAFLD appears not to be as asymptomatic as previously thought. The number
and severity of symptoms reported by children with NAFLD was higher than
anticipated. To what extent these symptoms are a direct result of NAFLD is unclear.
Symptoms, in particular the symptom of fatigue, were associated with reduced QOL in
children with NAFLD. Fatigue was the only symptom independently associated with
both QOL score and impaired QOL. Fatigue is associated with an imbalance of sleep,
stress, and/or psychological coping skills and has a profound negative effect on one’s
well-being. For many chronic medical conditions, fatigue is regarded as one of the
most debilitating symptoms experienced.(32-34) In adults with NAFLD, fatigue was
shown to be greater compared to healthy controls and similar to that of adults with
primary biliary cirrhosis.(10) While fatigue has been described as occurring in
children and adolescents with NAFLD,(35) the frequency and potential effects of
fatigue had not previously been assessed.

The frequency of fatigue in children with NAFLD, 68% in the NASH CRN,
appears to be greater than in healthy children. In a nationally representative sample,
fatigue was reported in 15% of boys and 25% of girls in grades 7 to 12.(36) Although
the majority of children with NAFLD are obese, obesity may not be the cause of
fatigue in children with NAFLD. Prospective studies in children and adolescents have
shown that obesity is not independently associated with either incident or persistent
fatigue.(37,38) Moreover, in the current sample, the severity of obesity as measured
by BMI Z score was not associated with QOL nor the symptoms experienced.
Whatever the cause, fatigue was very common in these children and was associated with decreased QOL.

Fatigue may be thought of as biopsychosocial complex of conditions with many components beyond general fatigue. When viewed in this framework many of the symptoms reported by children with NAFLD may not be unrelated but rather fit into a rubric as has been previously proposed for fatigue.(39-41) Thus, the symptoms in addition to fatigue that were significantly associated with QOL and impaired QOL can be classified as neuropsychological (trouble sleeping, trouble concentrating, sadness) and physical (nausea) symptoms associated with fatigue. In adults, structured exercise programs have been shown to have a positive impact on fatigue associated with medical conditions as well as fatigue experienced by healthy individuals.(42-49) Structured exercise may also be beneficial for fatigue in children with NAFLD, and exercise is already recommended in the treatment of NAFLD. Whether fatigue is a meaningful deterrent to exercise in children with NAFLD is unknown; future studies should consider this possibility as well as test exercise as a treatment for fatigue and QOL in children with NAFLD.

The multi-center design of the NASH CRN and the recruitment of subjects from a variety of settings make these results generalizable to children and adolescents in the United States with a clinical diagnosis of NAFLD. The timing of the development of NAFLD, the development of symptoms, and the impairment of QOL cannot be determined from a cross-sectional study. Despite the large sample size, the smaller number of girls was also an important limitation. While this is to be expected given the epidemiology of pediatric NAFLD, future studies should endeavor to
include a larger number of girls in order to characterize NAFLD in girls in more detail.

In summary, children with NAFLD have a decrement in QOL relative to healthy children. Given the high prevalence of pediatric NAFLD, this finding portends a potentially large number of children at risk for poor QOL. Symptoms, particularly fatigue, are common in children with NAFLD, and are a major determinant of both QOL score and impaired QOL. It remains unclear whether fatigue in children with NAFLD is related to liver disease itself or some other aspect of the metabolic syndrome phenotype. The care of children with NAFLD should be broadened to include evaluation of both symptoms and QOL. Future studies must delineate the mechanism of decreased QOL in children with NAFLD and develop interventions to restore and optimize QOL in children with NAFLD.
2.6 Acknowledgements

Chapter 2, in part, was presented as a poster at NASPGHAN, in San Diego, CA on November 14, 2008. The dissertation author was the first author of this poster: Kristin David, Jean Molleston, Aynur Unalp-Arida, Jeffrey B. Schwimmer, and the NASH CRN Research Group: “Health related quality of life in children with nonalcoholic fatty liver disease: Baseline data from the NASH CRN.” Abstract #63.

Chapter 2 has been submitted for publication of the material as it may appear in Hepatology, 2009. The dissertation author was the first author of this paper: Kristin D. Kistler, Jean Molleston, Aynur Unalp-Arida, Jeffrey B. Schwimmer, and the NASH CRN Research Group. Health related quality of life in children with nonalcoholic fatty liver disease: Baseline data from the NASH CRN.
2.7 Chapter 2 References


Chapter 3: Physical Activity Recommendations, Exercise Intensity, and Histological Severity of Nonalcoholic Fatty Liver Disease

3.1 Abstract

Factors that determine disease severity in NAFLD are unclear, but exercise is a recommended treatment. We evaluated the association between physical activity intensity and histological severity of NAFLD.

Adult patients with biopsy-proven NAFLD enrolled in the NASH Clinical Research Network reported time spent in leisure physical activity and were classified as sedentary (56%), or as meeting the U.S. guidelines for either moderate exercise (19%) or vigorous exercise (26%). Histology was reviewed by a central pathology committee. Frequency and odds of steatohepatitis (NASH) and advanced fibrosis were compared between subjects who met or did not meet exercise recommendations, and by mean total MET minutes per week (0; >0 - <500; ≥500).

A total of 609 adults (M=232, F=377) with NAFLD were included, with a mean age of 48 years. Neither moderate intensity exercise nor MET minutes per week were associated with a difference in the frequency of NASH or the stage of fibrosis. The frequency of NASH was significantly (p=0.003) lower in subjects who met (69%) vs. did not meet vigorous exercise recommendations (79%), and meeting vigorous recommendations was associated with a decreased adjusted odds of having NASH (OR: 0.58, p=0.04). Doubling the recommended time spent in vigorous exercise, as is suggested for achieving additional health benefits, was associated with a decreased adjusted odds of advanced fibrosis (OR: 0.39, p=0.02).
These data support an association of vigorous but not moderate or total exercise with the severity of NAFLD. Optimal doses of exercise by duration and intensity for the prevention or treatment of NASH have not been established; however, intensity may be more important than duration or total volume.

3.2 Introduction

Nonalcoholic fatty liver disease (NAFLD) is increasingly recognized as an important public health problem. NAFLD is the most common chronic liver disease in the United States.(1,2) From epidemiological surveys, it is estimated that up to 30% of the general population has NAFLD.(1-5) The full spectrum of NAFLD ranges from isolated steatosis to steatohepatitis (NASH), fibrosis, and cirrhosis. Obesity and insulin resistance are well-established risk factors for NAFLD; however, the pathogenesis of NAFLD is incompletely understood and factors that determine disease severity remain unclear.

Exercise is a major component of treatment for NAFLD as recommended by the American Gastroenterological Association and American Association for the Study of Liver Diseases.(6) These recommendations are based upon the relationship of NAFLD to obesity and insulin resistance. However, there is a lack of published data on the effectiveness of physical activity in the treatment of NAFLD. The studies that have examined physical activity and NAFLD severity are limited by use of surrogate markers for NAFLD, small sample sizes, and/or multimodal treatments, obscuring interpretation of the effects of physical activity from other interventions (e.g., diet modification).(7-15) A recent small study that included 37 individuals with
biopsy-proven NAFLD found no significant association between current physical activity level (categorized as active, some activity or inactive) and histological severity. (16) Contrary to expectations, participants with mild steatosis reported a significantly lower average historical exercise intensity compared to participants with moderate or severe steatosis. (16) Information on the relationship between physical activity and histological severity of NAFLD is thus limited. As there currently are no noninvasive markers that can adequately replace biopsy evaluation for presence and severity of the lesions of NASH, data with biopsy findings are important to improve understanding of the role of physical activity in the treatment of NAFLD.

As shown in table 3.1, federal guidelines from the U.S. Department of Health and Human Services (DHHS) and the U.S. Department of Agriculture (USDA) recommend that adults engage in at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity physical activity per week to improve and maintain health. (17) Doubling these amounts was found to produce additional health benefits. Controversy remains over the role played by exercise intensity versus total volume, and dose-response relationships differ across health outcomes. (17) In the context of the U.S. guidelines for exercise, we evaluated the association of exercise intensity and total volume of physical activity with histological severity of NAFLD using data from a large multi-center study, the NASH Clinical Research Network.
Table 3.1. DHHS and USDA Recommendations for Physical Activity in Adults

<table>
<thead>
<tr>
<th></th>
<th>Moderate Physical Activity</th>
<th>Vigorous Physical Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum Targets</td>
<td>≥150 minutes a week</td>
<td>≥75 minutes a week</td>
</tr>
<tr>
<td>Targets for more extensive</td>
<td>≥ 300 minutes a week</td>
<td>≥ 150 minutes a week</td>
</tr>
<tr>
<td>health benefits</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DHHS and USDA recommendations for physical activity in adults can be met by achieving ≥ 150 minutes a week of moderate physical activity or ≥ 75 minutes a week of vigorous physical activity. To achieve additional and more extensive health benefits the guidelines recommend increasing time spent in moderate physical activity to ≥ 300 minutes a week or increasing time spent in vigorous physical activity to ≥ 150 minutes a week.

3.3 Methods

3.3.1 Subjects

Details on the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) have been previously reported.(18,19) For these analyses we included baseline data from adult subjects enrolled in 2 NASH CRN studies: (1) the NAFLD Database, an observational cohort study; and (2) a clinical trial, PIVENS (NCT00063622). (20) Study protocols were approved by all participating center IRBs and an independent Data and Safety Monitoring Board. Each participant provided written informed consent.

We then included adults with liver biopsies available for central reading that were obtained within 2 years of enrollment, who had 5% or greater steatosis with or without any inflammation or fibrosis. Participants with incomplete histology data (n=435), steatosis in <5% of hepatocytes (n=49), or biopsy greater than 2 years from study enrollment (n=132) were excluded from the analyses.
3.3.2 Measures

3.3.2.1 Demographics

Demographic information collected during screening interviews as part of the registration process included age, gender, highest educational level achieved, and annual income.

3.3.2.2 Anthropometrics

Weight and height were measured with participants standing wearing light clothing. Body mass index (BMI) was calculated as the weight (kg) divided by the height (meters) squared, and categorized as normal (BMI 18.5-24.9 kg/m²), overweight (BMI 25-29.9 kg/m²), mild obesity (BMI 30-34.9 kg/m²), moderate obesity (BMI 35-39.9 kg/m²), and severe obesity (BMI > 40 kg/m²) according to the NIH and WHO classifications.(21,22)

3.3.2.3 Histology

The NASH CRN Pathology Committee (23) centrally reviewed liver biopsy slides from participants according to the published scoring system.(23) Steatosis was scored according to amount (%) of biopsy occupied. A diagnosis of NAFLD required the presence of ≥ 5% steatosis. Histologic features of NAFLD were assessed according to the validated system published by the Central Pathology Committee.(23) Fibrosis was staged as follows: a) stage 1a and 1b with zone 3 perisinusoidal fibrosis, delicate (requiring trichrome stain) and dense, respectively; b) 1c is portal only; c)
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stage 2 with zone 3 perisinusoidal plus periportal fibrosis; d) stage 3 is bridging fibrosis; and e) stage 4 is cirrhosis. The following diagnostic determinations were assigned: biopsies were categorized as: definitely not steatohepatitis, borderline steatohepatitis (zone 1 or zone 3 pattern), or definite steatohepatitis.

3.3.2.4 Physical Activity

Physical activity was measured by self-report using the physical activity questionnaire from the National Health and Nutrition Examination Survey (NHANES).(24) Participants reported time spent per week in specified recreational activities; a free-text field was also available for participants to report additional recreational activities. The following 19 recreational activities (plus free-text responses) were considered: swimming, jogging, running, brisk walking, bicycling on hills, bicycling on flat surfaces, hiking or climbing, aerobics, dancing, calisthenics, weight lifting, using a treadmill or step machine, golfing, singles tennis, doubles tennis, basketball, football, and soccer. Activities were assigned metabolic equivalent (MET) values based on a standard reference.(25) One (1) MET is the rate of energy expenditure while at rest. Activities with MET values between 3 and 5.9 were classified as moderate-intensity and activities with MET values ≥ 6 were classified as vigorous-intensity.(25) MET minutes per week was calculated as: MET value x minutes spent per week in activity.

Participants were categorized into the following groups based on the federal recommendations (17): 1) sedentary (those who met neither the recommendations for moderate or vigorous physical activity); 2) those who met the moderate physical
activity recommendations but did not meet the vigorous recommendations; 3) those who met the vigorous recommendations; subjects in this group could have met both the moderate and vigorous recommendations or the vigorous recommendations and not moderate recommendations. Subjects who had $\geq 500$ MET-minutes per week but did not meet either moderate or vigorous recommendations were excluded. Subjects in groups 2 and 3 were further categorized into 2a) those who met the recommendations for additional health benefits for moderate intensity exercise, and 3a) those who met the recommendations for additional health benefits for vigorous intensity exercise.

### 3.3.3 Data analysis

Descriptive statistics (mean, median, percentiles, standard deviation, range) were used to characterize the sample. Analysis of variance and Tukey’s post-hoc test were used to compare normally distributed characteristics between the sedentary, moderate, and vigorous groups. The Kruskal-Wallis test was used to compare non-normally distributed characteristics between the groups and the Mann-Whitney test was used to for pair wise comparisons in the event the Kruskal-Wallis test was significant. The unadjusted association between meeting moderate and vigorous physical activity recommendations, meeting the recommendations for additional health benefits, and the association between MET minutes per week (categorized as no MET minutes per week, $>0$ and $< 500$ MET minutes per week, and $\geq 500$ MET minutes per week) and odds of NASH, and odds of advanced fibrosis (no fibrosis, mild to moderate, bridging fibrosis or cirrhosis) were evaluated using a Chi Square
test; the adjusted (for age [18-30, 31-40, 41-50, 51-60, ≥61], gender, education [<HS; HS; some college; bachelors or higher]), annual household income [<29,999; 30,000-49,000; ≥50,000], BMI [≤29.9; 30-34.9; 35-39.9; ≥40], and glucose [mg/dL]) association for odds of NASH were evaluated using logistic regression. The Hosmer and Lemeshow Goodness-of-Fit Test was used to assess model fit. The adjusted association for odds of advanced fibrosis was evaluated using multinomial logistic regression. Pearson and deviance goodness of fit tests were used to assess model adequacy. The significance associated with the ability of meeting recommendations to distinguish between fibrosis categories was not evaluated unless an overall significant (p<0.10) relationship between meeting recommendations and advanced fibrosis was observed in the likelihood ratio test. We checked for multicollinearity among factors by ensuring all standard errors for the b coefficients were < 2.0. A p-value of < 0.05 was defined as significant for individual factors in the logistic models.

3.4 Results

3.4.1 Subjects’ Baseline Characteristics

There were 1,266 adults enrolled in the NASH CRN as of January 2008, of these 609 met inclusion/exclusion criteria and were included in the analysis (Figure 3.1). The mean age was 48 ± 12 years and 62% were female. Overall, 73% of participants were obese including 30% mild, 25% moderate, and 18% severe. Type 2 diabetes was present in 23%. Sixty-one percent (369/609) had definite NASH, 20% (124/609) had borderline NASH, and 19% (116/609) had NAFLD without NASH.
Twenty-four (147/609) percent had no fibrosis, 50% (307/609) had mild to moderate while 26% had bridging fibrosis or cirrhosis (155/609).

Figure 3.1. Inclusion and Exclusion Flow Chart
3.4.2 Distribution of Physical Activity Levels

Fifty-six percent of participants (339/609) were considered sedentary; of those 33% (202/609) reported no time spent in recreational physical activity and 23% (137/609) reported participation in some recreational physical activity but not enough to meet either of the recommendations. Thus 44% (270/609) of participants met either the recommendations for moderate or vigorous physical activity.

Moderate physical activity recommendations were met by 19% (114/609) of participants. Brisk walking was the most common moderate intensity activity reported. Among participants who met moderate activity recommendations, the median (interquartile range) hours per week of moderate physical activity was 4.5 (3.4 – 7.0). The median (interquartile range) total MET hours per week was 20.2 (13.6 – 30.4) and the median (interquartile range) total hours spent per week in any physical activity was 5.0 (3.5 – 7.5). Among participants who met moderate activity recommendations, 48% (55/114) also met recommendations for additional health benefits for moderate intensity exercise.

Vigorous physical activity recommendations were met by 26% (156/609) of participants. Fifty-two percent (81/156) of subjects in this group met both the moderate and vigorous recommendations while 48% (75/156) met vigorous recommendations and not moderate recommendations. Running on a treadmill and/or using a step machine were the most common vigorous intensity activities reported. Of the subjects who met the vigorous recommendations, the median (interquartile range) hours per week spent in vigorous physical activity was 2.5 (2.0 – 4.0). The
median (interquartile range) total MET hours per week was 31.8 (19.4 – 51.1) and the median (interquartile range) total hours spent per week in any physical activity was 5.8 (3.0 – 9.0). Among participants who met vigorous activity recommendations, 48% (55/114) also met recommendations for additional health benefits for vigorous intensity exercise.

Table 3.2 displays the sample characteristics by activity categories - sedentary, moderate, and vigorous. Women were more likely to be sedentary than men. Participants who met recommendations for vigorous physical activity were significantly younger, had lower BMI, and had lower glucose than both participants who met moderate but not vigorous recommendations, and participants who were sedentary. Sedentary participants had significantly less education and significantly lower annual household income than participants who met either moderate or vigorous recommendations.

### Table 3.2 Characteristics of Subjects who are Sedentary, Met Moderate Recommendations, or Met Vigorous Recommendations

<table>
<thead>
<tr>
<th></th>
<th>All Subjects (n=609)</th>
<th>Sedentary (N = 339)</th>
<th>Moderate (N = 114)</th>
<th>Vigorous (N = 156)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (mean [SD])</td>
<td>47.7 (12.0)</td>
<td>48.5 (11.6)a</td>
<td>50.5 (11.6)b,c</td>
<td>44.1 (12.5)c</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Gender</strong>, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>377 (61.9)</td>
<td>232 (68.2)a,c</td>
<td>62 (54.4)b</td>
<td>83 (53.5)b</td>
<td>0.001*</td>
</tr>
<tr>
<td>Male</td>
<td>232 (38.1)</td>
<td>107 (31.6)</td>
<td>52 (45.6)</td>
<td>72 (46.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Education</strong>, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; High school</td>
<td>55 (9.0)</td>
<td>41 (12.1)a,c</td>
<td>10 (8.8)b</td>
<td>4 (2.6)b</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>
Table 3.2 Characteristics of Subjects who are Sedentary, Met Moderate Recommendations, or Met Vigorous Recommendations continued

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects (n=609)</th>
<th>Sedentary (N = 339)</th>
<th>Moderate (N = 114)</th>
<th>Vigorous (N = 156)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High school grad</td>
<td>131 (21.5)</td>
<td>86 (25.4)</td>
<td>20 (17.5)</td>
<td>25 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>227 (37.3)</td>
<td>129 (38.1)</td>
<td>40 (35.1)</td>
<td>58 (37.4)</td>
<td></td>
</tr>
<tr>
<td>≥ Bachelors</td>
<td>195 (32.0)</td>
<td>83 (24.5)</td>
<td>44 (38.6)</td>
<td>68 (43.9)</td>
<td></td>
</tr>
<tr>
<td>Income, n (%)</td>
<td>115 (19.4)</td>
<td>82 (24.5)a,c</td>
<td>14 (12.4)b</td>
<td>22 (14.5)b</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>&lt;$29,999</td>
<td>128 (21.0)</td>
<td>85 (25.4)</td>
<td>20 (17.7)</td>
<td>23 (15.1)</td>
<td></td>
</tr>
<tr>
<td>≥$50,000</td>
<td>354 (58.1)</td>
<td>168 (50.1)</td>
<td>79 (69.9)</td>
<td>107 (70.4)</td>
<td></td>
</tr>
<tr>
<td>BMI, n (%)</td>
<td>161 (26.4)</td>
<td>77 (23.0)c</td>
<td>24 (21.2)c</td>
<td>30 (19.9)d</td>
<td>0.001*</td>
</tr>
<tr>
<td>30-34.9</td>
<td>184 (30.2)</td>
<td>101 (30.1)</td>
<td>32 (28.3)</td>
<td>51 (32.7)</td>
<td></td>
</tr>
<tr>
<td>35-39.9</td>
<td>152 (25.0)</td>
<td>90 (26.9)</td>
<td>35 (31.0)</td>
<td>27 (17.3)</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>107 (17.6)</td>
<td>67 (20.0)</td>
<td>22 (19.5)</td>
<td>18 (11.5)</td>
<td></td>
</tr>
<tr>
<td>T2 Diabetes, n (%)</td>
<td>137 (22.5)</td>
<td>89 (26.3)c</td>
<td>26 (22.8)</td>
<td>22 (14.1)</td>
<td>0.011*</td>
</tr>
<tr>
<td>Mean</td>
<td>939.4 (1345.0)</td>
<td>105.0 (152.8)a,c,e</td>
<td>1440.7 (813.5)a,c,e</td>
<td>2386.1 (1657.9)a,b</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MET/min/wk (SD)</td>
<td>61.0 (41–92)</td>
<td>61.0 (41–92)</td>
<td>62.0 (38–92)</td>
<td>61.0 (42–91)</td>
<td>0.978†</td>
</tr>
<tr>
<td>Median (IQR):</td>
<td>43.0 (31–63)</td>
<td>44.0 (32–65)</td>
<td>44.0 (31–61)</td>
<td>42.0 (31–60)</td>
<td>0.605†</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>47.0 (30–82)</td>
<td>49.0 (32–87)</td>
<td>43.5 (28–68)</td>
<td>47.0 (28–73)</td>
<td>0.151†</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>148.0 (106–207)</td>
<td>146 (108–205)</td>
<td>169.5 (104–230)</td>
<td>144.0 (105–192)</td>
<td>0.159†</td>
</tr>
</tbody>
</table>
Table 3.2 Characteristics of Subjects who are Sedentary, Met Moderate Recommendations, or Met Vigorous Recommendations continued

<table>
<thead>
<tr>
<th></th>
<th>All Subjects (n=609)</th>
<th>Sedentary1 (N = 339)</th>
<th>Moderate2 (N = 114)</th>
<th>Vigorous3 (N = 156)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL (mg/dL)</td>
<td>43.0 (36–50)</td>
<td>43.0 (36–50)</td>
<td>41.0 (36–53)</td>
<td>43.0 (36–52)</td>
<td>0.962†</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>119.0 (96–143)</td>
<td>121.0 (97–144)</td>
<td>117.0 (91–139)</td>
<td>119.0 (96–142)</td>
<td>0.263†</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>98.0 (87–114)</td>
<td>101 (88–116)c</td>
<td>98.0 (87–113)</td>
<td>94.0 (84–107)b</td>
<td>0.005†</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>18.4 (12–29)</td>
<td>20.0 (13–29)c</td>
<td>19.4 (13–32)c</td>
<td>14.0 (8–27)ab</td>
<td>0.012†</td>
</tr>
</tbody>
</table>

1 Subjects not meeting moderate or vigorous physical activity recommendations; 2 ≥150 minutes moderate-intensity physical activity/week; 3 ≥75 minutes vigorous-intensity physical activity/week

† Significantly different from Moderate group; b Significantly different from Sedentary group;
c Significantly different from Vigorous group; * P-value is from comparison of sedentary, moderate and vigorous groups, and from ANOVA (continuous data; pair wise comparisons were conducted using the Tukey test) or Chi-Square test (categorical variables); SD: Standard Deviation; IQR: Interquartile Range; † P-value is from comparison of sedentary, moderate and vigorous groups from Kruskal-Wallis test, pair wise comparisons were conducted using the Mann-Whitney test.

3.4.3 Association between Recommendations and NAFLD Severity

3.4.3.1 Steatohepatitis

The frequency of NASH was not significantly (p = 0.35) different between subjects who met the recommendations for moderate physical activity (83%) and those who were sedentary (78%), or between individuals who met the recommendation for additional health benefits for moderate physical activity (84%) and those who were sedentary (78%) (p=0.39).

The frequency of NASH was significantly (p=0.03) lower in subjects who met recommendations for vigorous physical activity (69%) versus those who did not meet this recommendation (79%). After adjusting for demographic, socioeconomic and clinical characteristics, meeting vigorous physical activity recommendations was still
associated with a significantly (p=0.04) decreased odds of having NASH (OR: 0.58 [95% CI 0.35-0.97]) (Figure 3.2). There was no significant interaction between gender and meeting vigorous recommendations (p=0.06), an interaction term was therefore not included in the model. The estimated odds of NASH was even lower in participants (n=88) who met the additional health benefits for vigorous physical activity recommendation of ≥ 150 MET minutes per week (OR: 0.45 [0.25-0.84] p=0.01)

Figure 3.2. Adjusted odds (Log scale) and 95% confidence interval of NASH for participants who met vigorous physical activity recommendations compared to not meeting vigorous recommendations, and adjusted odds and 95% confidence interval of NASH for participants who met moderate physical activity recommendations compared to sedentary participants. Odds ratios adjusted for: age, gender, BMI, income, education and glucose.
3.4.3.2 Advanced fibrosis

Neither meeting moderate physical activity recommendations (p=0.69), nor the recommendations for additional health benefits for moderate physical activity (p=0.83) were associated with the degree of fibrosis. In contrast, meeting vigorous physical activity recommendations was associated with a significantly (p=0.003) lower odds of advanced fibrosis compared to no fibrosis (OR: 0.45 [0.26-0.76]) in the univariate analysis. After adjusting for demographic, socioeconomic and clinical characteristics, however, this association was no longer significant (p-value from likelihood ratio test = 0.25). Meeting the additional vigorous physical activity recommendation was associated with a significantly lower odds of advanced fibrosis versus no fibrosis (OR: 0.39 [0.18-0.88], p=0.023) even after adjustment for demographic, socioeconomic and clinical characteristics.

3.4.3.3 MET minutes per week

There was no significant (p=0.53) difference in the frequency of NASH between the participants with no MET minutes per week (79%), >0 and < 500 MET minutes per week (76%), and ≥ 500 MET minutes per week (74%). Nor was there a significant (p=0.28) difference in the frequency of advanced fibrosis NASH between the participants with no MET minutes per week (25%), >0 and < 500 MET minutes per week (31%), and ≥ 500 MET minutes per week (23%).
3.5 Discussion

In a large multicenter study that has accrued patients from across the United States, we assessed the cross sectional relationship between meeting or exceeding U.S. national guidelines for physical activity and histological severity of NAFLD. There was no association between meeting moderate physical activity guidelines and histological severity of NAFLD. Meeting the minimum guidelines for vigorous physical activity was associated with a significant reduction in the adjusted odds of having NASH. Furthermore, exceeding the vigorous physical activity guidelines, which is recommended for additional health benefits (DHHS), was associated with a decreased odds of fibrosis. The main conclusion from the study is that regular vigorous physical activity is likely to have more benefit for severity of NAFLD than total volume of physical activity.

There is a large amount of literature that shows moderate, vigorous, and total volume of physical activity is related to a wide range of health outcomes. Dose-response (i.e., combination of intensity and duration) relationships vary substantially by outcome but evidence for a dose-response relationship has been demonstrated for all-cause mortality, cardiovascular disease, colon cancer. However, based on the available data it is difficult to discern the effects of physical activity intensity versus duration on health outcomes. Vigorous physical activity appears to be more beneficial for some outcomes such as cardiovascular disease and premature mortality, and this appears to be the case for NAFLD. The epidemiological studies on exercise intensity and cardiovascular outcomes are better developed for men than women. In
men, the preponderance of evidence suggests that physical activity of vigorous intensity, but not moderate intensity is associated with a decreased frequency of coronary heart disease (CHD). (28-29) For example, The Health Professionals’ Follow-up Study, with a sample of 44,452 men and 12 years follow-up, demonstrated that, adjusted for exercise volume, vigorous but not moderate physical activity was associated with a decreased risk for myocardial infarction. (30) In addition to cardiovascular disease, large long-term studies of men have shown that vigorous but not moderate intensity physical activity is associated with decreased risk for all-cause mortality. (31-33) Less is known about the effect of exercise intensity on health outcomes in women because there are fewer published data and the available studies have much shorter follow-up duration. A large study, however, reported a similar risk reduction for coronary events for moderate and vigorous activity. (34) Thus data from men suggest important differences between exercise intensity and risk for CHD while more data with longer follow-up are needed to see if the same relationship exists in women. In the current study no gender interaction was found in the analysis of meeting vigorous recommendations and odds of NASH.

The biological basis for differences between moderate and vigorous physical activity effects on severity of NAFLD are not known, however there are plausible explanations. One potential explanation is the effect of exercise on AMP-activated protein kinase (AMPK), a regulator of intracellular energy metabolism. AMPK activation in the liver increases fatty acid oxidation and decreases glucose production. (35) Activation of AMPK leads to phosphorylation of many downstream targets that regulate mitochondrial biogenesis and hepatic gluconeogenesis, e.g.
peroxisome proliferator-activated receptor \(\gamma\) coactivator-\(1\alpha\) (PGC-1\(\alpha\)). (36)

Furthermore, AMPK not only regulates energy but may also play a key role in hepatic fibrogenesis. AMPK has been shown to suppress hepatic stellate cell proliferation and thus influence fibrosis. Under normal conditions, AMPK is activated when the ratio of AMP is greater than ATP. Physical activity is a circumstance that can increase the AMP to ATP ratio; however, only vigorous physical activity results in a large enough shift of the AMP to ATP ratio required to activate AMPK. Thus, the observed differences in the association between exercise intensity and histological severity could be due to differences in the ability of exercise to modulate cellular pathways controlling metabolism, inflammation and matrix deposition. (37)

While current treatment recommendations for NAFLD include dietary modification and exercise, data are lacking on the effectiveness of diet modification and exercise, separately or combined, in decreasing NAFLD severity. Present recommendations are predicated upon the relationship between NAFLD and obesity and insulin resistance, with diet and exercise recommendations designed to produce weight loss. A systematic review of published studies on the effectiveness of weight reduction for the treatment of NAFLD found that there was inadequate information to support or refute the treatment recommendation of weight loss. (38) Although exercise has been included in multi-modal interventions (7-15) there are no published data assessing the histological response to exercise. The results from the present study highlight the importance of linking recommendations to outcomes and suggest that following the physical activity recommendations for NAFLD in their current form may not be a sufficient approach. These data suggest that not all exercise is equal in
terms of its potential impact on disease severity and that moderate intensity physical activity may not be adequate treatment for NAFLD. Future studies should be designed to corroborate or refute the results suggested from the cross sectional data from this study. If causal relationships between vigorous but not moderate physical activity and NAFLD severity are identified, the current recommendations should be amended to reflect the new knowledge.

The multi-center design of the NASH CRN and the recruitment of subjects from a variety of settings make these results generalizable to adults in the U.S. with a clinical diagnosis of NAFLD. An additional strength of this study was the inclusion of liver histology on all patients with a rigorous, standardized, central biopsy review. A limitation was the cross sectional nature of the study; thus we cannot determine cause and effect from these data. In addition, self report of physical activity may result in error and misclassification. In particular, better reliability and validity has been demonstrated for the recall of vigorous intensity physical activity versus moderate intensity physical activity.(39-41) This differential reliability and validity could have reduced power to detect associations with moderate physical activity. Longitudinal studies with objective measures of physical activity are recommended to further examine the relationship between physical activity intensity and histologic severity in individuals with NAFLD.

In conclusion, in this study we found a relationship between leisure time physical activity and NAFLD severity. This relationship was limited to vigorous and not moderate intensity activity. Total volume of physical activity also was not related to outcomes. Thus, intensity may be an important dimension of physical activity that
needs to be considered when counseling patients and planning interventions. While
this study showed that vigorous intensity exercise may afford greater benefits in
individuals with NAFLD compared to moderate-intensity exercise, the difficulty of
enabling a population of overweight adults with NAFLD to be able to safely and
consistently perform vigorous exercise presents a clinical challenge. Studies are
needed to better understand the mechanisms that underlie the potential differential
effects of vigorous versus moderate activity. Intervention studies with validated
measures of physical activity are needed to confirm the differential effects of vigorous
versus moderate activity on NAFLD severity. Although recommended for treatment
for NAFLD, physical activity is an unproven therapy; these data suggest that not all
activities can be expected to have same therapeutic benefit.
3.6 Acknowledgements

Chapter 3 has been submitted for publication of the material as it may appear in Annals of Internal Medicine, 2009. The dissertation author was the first author of this paper: Kristin D. Kistler, Elizabeth M. Brunt, Jeanne M. Clark, Anna Mae Diehl, James F. Sallis, Jeffrey B. Schwimmer, and the NASH CRN Research Group. Physical Activity Recommendations, Exercise Intensity, and Histological Severity of Nonalcoholic Fatty Liver Disease.
3.7 Chapter 3 References


17. 2008 Physical Activity Guidelines for Americans. U.S. Dept. of Health and Human Services


